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NEWS 7	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 8	JUN 06	EPFULL enhanced with 260,000 English abstracts
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NEWS 10	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 11	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS 12	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data
NEWS 13	JUN 30	AEROSPACE enhanced with more than 1 million U.S. patent records
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NEWS 15	JUN 30	STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in
NEWS 16	JUN 30	STN AnaVist enhanced with database content from EPFULL
NEWS 17	JUL 28	CA/CAplus patent coverage enhanced
NEWS 18	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS 19	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 20	JUL 28	STN Viewer performance improved
NEWS 21	AUG 01	INPADOCDB and INPAFAMDB coverage enhanced
NEWS 22	AUG 13	CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS 23	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS 24	AUG 15	CAplus currency for Korean patents enhanced
NEWS 25	AUG 25	CA/CAplus, CASREACT, and IFI and USPAT databases enhanced for more flexible patent number searching
NEWS 26	AUG 27	CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information

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                                                         ENTRY    SESSION
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DICTIONARY FILE UPDATES:   2 SEP 2008  HIGHEST RN 1045894-64-1

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=>
Uploading C:\Program Files\STNEXP\Queries\pain.str
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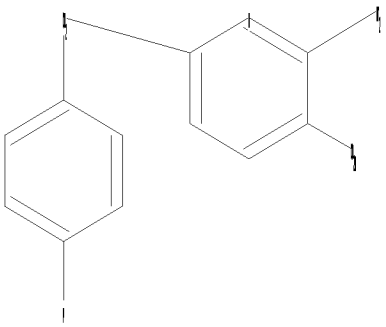

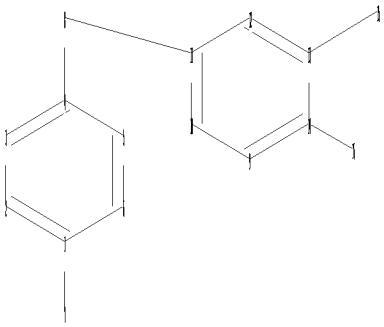

chain nodes :
7 8 15 16
ring nodes :
1 2 3 4 5 6 9 10 11 12 13 14
chain bonds :
1-7 4-8 8-11 13-15 14-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14
exact/norm bonds :
13-15
exact bonds :
1-7 4-8 8-11 14-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

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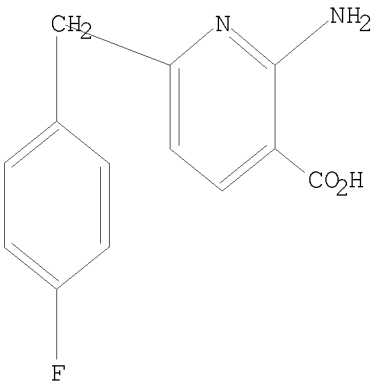
L1 STR



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=> s l1
SAMPLE SEARCH INITIATED 16:00:49 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED        1 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

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                                                       ENTRY    SESSION
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COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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http://www.cas.org/support/stngen/stndoc/properties.html

=> s flupirtine/cn
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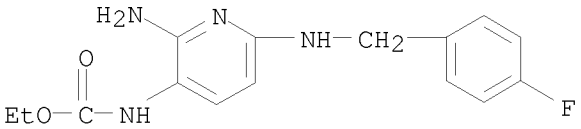
L3 1 FLUPIRTINE/CN

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2008 ACS on STN
RN 56995-20-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Carbamic acid, N-[2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [2-amino-6-[[(4-fluorophenyl)methyl]amino]-3-pyridinyl]-, ethyl ester (9CI)
OTHER NAMES:
CN D 9998
CN Flupirtine
CN Katadolon
CN Trancopal Dolo
MF C15 H17 F N4 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

157 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
158 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medicine
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FULL ESTIMATED COST	7.61	8.95

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FILE 'DDFU' ACCESS NOT AUTHORIZED

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FILE 'DRUGB' COULD NOT BE ENTERED

FILE 'DRUGMONOG2' ENTERED AT 16:02:45 ON 03 SEP 2008

FILE 'DRUGU' COULD NOT BE ENTERED

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FILE 'PASCAL' COULD NOT BE ENTERED

FILE 'PCTGEN' COULD NOT BE ENTERED

FILE 'PHARMAML' COULD NOT BE ENTERED

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FILE 'PHIN' ENTERED AT 16:02:45 ON 03 SEP 2008

FILE 'SCISEARCH' ENTERED AT 16:02:45 ON 03 SEP 2008

FILE 'TOXCENTER' ENTERED AT 16:02:45 ON 03 SEP 2008

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FILE 'USPATOLD' ENTERED AT 16:02:45 ON 03 SEP 2008

FILE 'USPAT2' ENTERED AT 16:02:45 ON 03 SEP 2008

=> s l3 or flupirtine

'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
L4 1879 L3 OR FLUPIRTINE

=> s neuropath? (s) pain
L5 59357 NEUROPATH? (S) PAIN

=> s l4 and l5
L6 101 L4 AND L5

=> s opioid
L7 274294 OPIOID

=> s l6 and l7
L8 47 L6 AND L7

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=> dup rem
ENTER L# LIST OR (END):l8
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DRUGMONOG2, IMSPRODUCT'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L8
L9           40 DUP REM L8 (7 DUPLICATES REMOVED)

=> d l9 30-40 ibib, kwic

L9   ANSWER 30 OF 40  SCISEARCH  COPYRIGHT (c) 2008 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2004:357431  SCISEARCH
THE GENUINE ARTICLE: 810EK
TITLE:               Pharmacological characterisation of acid-induced muscle
                     allodynia in rats
AUTHOR:              Nielsen A N (Reprint); Mathiesen C; Blackburn-Munro G
CORPORATE SOURCE:    NeuroSearch AS, Dept Pharmacol, Pederstrupvej 93, DK-2750
                     Ballerup, Denmark (Reprint); NeuroSearch AS, Dept
                     Pharmacol, DK-2750 Ballerup, Denmark
COUNTRY OF AUTHOR:   Denmark
SOURCE:              EUROPEAN JOURNAL OF PHARMACOLOGY, (8 MAR 2004) Vol. 487,
                     No. 1-3, pp. 93-103.
                     ISSN: 0014-2999.
PUBLISHER:           ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM,
                     NETHERLANDS.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     38
ENTRY DATE:          Entered STN: 30 Apr 2004
                     Last Updated on STN: 30 Apr 2004
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       .  .  .  now characterised this model of muscoskeletal pain
     pharmacologically, by evaluating the antinociceptive effects of various
     analgesics after systemic administration.  The mu-opioid
     receptor agonist morphine (3 and 6 mg/kg) produced a particularly
     prolonged antiallodynic effect.  The glutamate receptor antagonists
     ([8-methyl-5-(4-(N,N-dimethylsulfamoyl)phenyl)-6,7,8,9,-tetrahydro-1H-
     pyrrolo[3,2-h]-iso-quinoline-2,3-dione-3-O-(4-hydroxybutyric
     acid-2-yl)oxime] NS1209 and ketamine (6 and 15 mg/kg, respectively), the
     KCNQ K+ channel openers retigabine and flupirtine (10 and 20
     mg/kg, respectively) and the Na+ channel blocker mexiletine (37.5 mg/kg)
     also significantly increased paw withdrawal threshold, although.  .  .
STP  KeyWords Plus (R): NA+ CHANNEL BLOCKERS; POTASSIUM CHANNELS;
     NEUROPATHIC PAIN; ANTICONVULSANT RETIGABINE;
     FIBROMYALGIA PATIENTS; RECEPTOR ANTAGONISTS; TEMPORAL SUMMATION;
     HYPERALGESIA; FLUPIRTINE; INJECTION

L9   ANSWER 31 OF 40  USPATFULL on STN                  DUPLICATE 4
ACCESSION NUMBER:       2003:119729  USPATFULL
TITLE:                  Topical compositions and methods for treating pain
INVENTOR(S):            Williams, Robert O., Austin, TX, UNITED STATES
                        Zhang, Feng, Austin, TX, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20030082214     A1   20030501
                        US 6638981         B2   20031028
```

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APPLICATION INFO.: US 2001-931293 A1 20010817 (9)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 57
EXEMPLARY CLAIM: 1
LINE COUNT: 2008
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Topical compositions and methods for treating pain. The invention provides oil-in-water emulsions comprising an antidepressant; an NMDA-receptor antagonists; a lipophilic component; water; and a surfactant. The compositions induce a local-anesthetic effect when topically administered to intact skin thereby treating or preventing pain, for example, neuropathic pain.

SUMM [0002] Pain results from the noxious stimulation of nerve endings. Nociceptive pain is caused by noxious stimulation of nociceptors (e.g., a needle stick or skin pinch), which then transmit impulses over intact neural pathways to the spinal neurons and then to the brain. Neuropathic pain is caused by damage to neural structures, such as damage to peripheral nerve endings or nociceptors, which become extremely sensitive to stimulation and can generate impulses in the absence of stimulation (e.g., herpes zoster pain after the rash has healed). Peripheral nerve damage can lead to pathological states where there is a reduction in pain threshold (i.e., allodynia), an increased response to noxious stimuli (hyperalgesia), or an increased response duration (persistent pain). GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 529 (Joel G. Hardman et al. eds., 9th ed. 1996); HARRISON'S PRINCIPLES. . .

SUMM [0005] N-methyl-D-aspartate ("NMDA") receptor antagonists, such as ketamine have local-aesthetic properties and topical administration is as an effective neuropathic pain treatment. See, for example, U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998). In another example, topical administration of antidepressant medications, such as amitriptyline, has been reported effective for neuropathic pain treatment. See, for example, U.S. Pat. No. 6,211,171 (issued Apr. 3, 2001); J. Sawynok et al., 82 PAIN 149 (1999). In addition, topical administration of a combination of a tricyclic antidepressant and an NMDA-receptor antagonist is reported to have excellent local-anesthetic properties when topically applied and is useful for treatment of neuropathic pain, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001).

SUMM . . . skin is routinely used to treat minor indications, it has not found significant use for treating more severe nociceptive and neuropathic pain because it is difficult to get significant concentrations through the skin barrier. Because of the skin's drug-permeation resistance, as little. . . (TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 7 (Tapash K. Ghosh et al. eds., 1997)). Another problem with topical administration of pain relievers is stability of the composition. Local-anesthetics emulsion compositions are inherently unstable, and phase separation can occur during shipment and. . .

SUMM [0009] The invention provides methods and topical compositions for treating or preventing pain. The compositions of the invention can be topically administered to intact skin to provide a local-anesthetic effect thereby treating or preventing pain,

for example, neuropathic pain. In one embodiment, the invention provides stable, skin penetrating compositions for topical administration comprising a combination of an antidepressant and. . .

SUMM . . . NMDA-receptor antagonist through intact skin at a high flux rate to induce local anesthesia and thereby treat, ameliorate, or prevent neuropathic pain. Furthermore, the compositions of the invention are stable both physically (resists coalescing of droplets and Ostwald ripening) and chemically stable. . .

SUMM . . . stimulation of peripheral nociceptors. The compositions and methods of the invention are effective to induce local anesthesia and to treat neuropathic pain. As used herein the term " neuropathic pain" refers to neuropathic-pain syndromes, that is, pain due to lesions or dysfunction in the nervous system. The compositions and methods of the invention can be used to treat or prevent pain related to or induced by the following diseases, trauma, or conditions: general neuropathic conditions, such as peripheral neuropathy, phantom pain, reflex-sympathetic dystrophy, causalgia, syringomyelia, and painful scar; specific neuralgias at any location of the body; back pain; diabetic neuropathy; alcoholic neuropathy; metabolic neuropathy; inflammatory neuropathy; chemotherapy-induced neuropathy, herpetic neuralgias; traumatic odontalgia; endodontic odontalgia; thoracic-outlet syndrome; cervical, thoracic, or lumbar radiculopathies with nerve compression; cancer with nerve invasion; traumatic-avulsion injuries; mastectomy, thoracotomy pain; spinal-cord-injury; stroke; abdominal-cutaneous nerve entrapments; tumors of neural tissues; arachnoiditis; stump pain; fibromyalgia; regional sprains or strains; myofascial pain; psoriatic arthropathy; polyarteritis nodosa; osteomyelitis; bums involving nerve damage; AIDS-related pain syndromes; connective tissue disorders, such as systemic lupus erythematosis, systemic sclerosis, polymyositis, and dermatomyositis; and inflammatory conditions, such as acute. . .

SUMM [0113] Other NMDA-receptor antagonists include, but are not limited to, amantadine, eliprodil, iamotrigine, riluzole, aptiganel, flupirtine, celfotel, levemopamil, 1-(4-hydroxy-phenyl)-2-(4-phenylsulfanyl-piperidin-1-yl)-propan-1-one; 2-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-1-naphthalen-2-yl-ethanone (E 2001); 3-(1,1-dimethyl-heptyl)-9-hydroxymethyl-6,6-dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (HU-211); 1-{4-[1-(4-chloro-phenyl)-1-methyl-ethyl]-2-methoxy-phenyl}-1H-[1,2,4]triazole-3-carboxylic acid amide (CGP 31358); acetic acid 10-hydroxy-7,9,7',9'-tetramethoxy-3,3'-dimethyl-3,4,3',4'-tetrahydro-1H, 1'H-[5,5']bi[benzo[g]isochromenyl]-4-yl ester (ES 242-1);. . .

SUMM [0148] As used herein the term "opioid" means all agonists and antagonists of opioid receptors, such as mu (μ), kappa (κ), and delta (δ) opioid receptors and subtypes thereof. For a discussion of opioid receptors and subtypes see GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 521-525 (Joel G. Hardman et al. eds., 9th ed. 1996), hereby expressly incorporated herein by reference. The opioid can be any opioid receptor agonist or antagonist known or to be developed. Preferred opioids interact with the μ- opioid receptor, the κ- opioid receptor, or both. Preferably, the opioid is an opioid-receptor agonist.

SUMM . . . pharmaceutically-acceptable salts thereof, or mixtures thereof,

all of which patents are hereby expressly incorporated herein by reference. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

L9 ANSWER 32 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2003:119740 USPATFULL		
TITLE:	Sterile, breathable patch for treating wound pain		
INVENTOR(S):	Mason, Paul Arthur, Flemington, NJ, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030082225	A1	20030501
APPLICATION INFO.:	US 2001-45730	A1	20011019 (10)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711		
NUMBER OF CLAIMS:	53		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1480		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0005] N-methyl-D-aspartate ("NMDA") receptor antagonists, such as ketamine also have local-anesthetic properties and topical administration is as an effective neuropathic pain treatment. See, for example, U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998). In another example, topical administration of antidepressant medications, such as amitriptyline, has been reported effective for neuropathic pain treatment. See, for example, U.S. Pat. No. 6,211,171 (issued Apr. 3, 2001); J. Sawynok et al., 82 PAIN 149 (1999). In addition, topical administration of a combination of a tricyclic antidepressant and an NMDA-receptor antagonist is reported to have excellent local-anesthetic properties when topically applied and is useful for treatment of neuropathic pain, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001).

SUMM [0043] As used herein the term "opioid" means all agonists and antagonists of opioid receptors, such as mu (μ), kappa (κ), and delta (δ) opioid receptors and subtypes thereof. For a discussion of opioid receptors and subtypes see GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 521-525 (Joel G. Hardman et al. eds., 9th ed. 1996), hereby expressly incorporated herein by reference. The opioid can be any opioid receptor agonist or antagonist known or to be developed. Preferred opioids interact with the opioid receptor, the κ- opioid receptor, or both. Preferably, the opioid is an opioid-receptor agonist.

SUMM . . . pharmaceutically-acceptable salts thereof, or mixtures thereof, all of which patents are hereby expressly incorporated herein by reference. The most preferred opioid is morphine or a pharmaceutically-acceptable salt thereof.

SUMM [0081] Other NMDA-receptor antagonists include, but are not limited to, amantadine, eliprodil, iamotrigine, riluzole, aptiganel, flupirtine, celfotel, levemopamil, 1-(4-hydroxyphenyl)-2-(4-phenylsulfanyl-piperidin-1-yl)-propan-1-one; 2-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-1-naphthalen-2-yl-ethanone (E 2001); 3-(1,1-dimethyl-heptyl)-9-hydroxymethyl-6,6-dimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (HU-211); 1-{4-[1-(4-chloro-phenyl)-1-

methyl-ethyl]-2-methoxy-phenyl}-1H-[1,2,4]triazole-3-carboxylic acid amide (CGP 31358); acetic acid 10-hydroxy-7,9,7',9'-tetramethoxy-3,3'-dimethyl-3,4,3',4'-tetrahydro-1H,1H-[5,5']bi[benzo[g]isochromenyl]-4-yl ester (ES 242-1); 14-hydroxy-11-isopropyl-10-methyl-5-octyl-10,13-diaza-tricyclo[6.6.1.04,15]pentadeca-1,4,6,8(15)-tetraen-12-one;. . .

SUMM . . . thereof. Another example of a mixture of local anesthetics useful in patches of the invention is a combination of an opioid and a sodium-channel blocker, such as a mixture of morphine or a pharmaceutically acceptable salt thereof and lidocaine or a. . .

SUMM . . . stimulation of peripheral nociceptors. The patches and methods of the invention are effective to induce local anesthesia and to treat neuropathic pain. As used herein the term "neuropathic pain" refers to neuropathic-pain syndromes, that is, pain due to lesions or dysfunction in the nervous system. The patches and methods of the invention can be used to treat or prevent pain related to or induced by the following diseases, trauma, or conditions: general neuropathic conditions, such as peripheral neuropathy, phantom pain, reflex-sympathetic dystrophy, causalgia, syringomyelia, and painful scar; specific neuralgias at any location of the body; back pain; diabetic neuropathy; alcoholic neuropathy; metabolic neuropathy; inflammatory neuropathy; chemotherapy-induced neuropathy, herpetic neuralgias; traumatic odontalgia; endodontic odontalgia; thoracic-outlet syndrome; cervical, thoracic, or lumbar radiculopathies with nerve compression; cancer with nerve invasion; traumatic-avulsion injuries; mastectomy, thoracotomy pain; spinal-cord-injury; stroke; abdominal-cutaneous nerve entrapments; tumors of neural tissues; arachnoiditis; stump pain; fibromyalgia; regional sprains or strains; myofascial pain; psoriatic arthropathy; polyarteritis nodosa; osteomyelitis; burns involving nerve damage; AIDS-related pain syndromes; connective tissue disorders, such as systemic lupus erythematosis, systemic sclerosis, polymyositis, and dermatomyositis; and inflammatory conditions, such as acute. . .

CLM What is claimed is:

. . . patch of claim 1, wherein the local anesthetic comprises a sodium-channel blocker, an antidepressant, an NMDA receptor antagonist, or an opioid, or a pharmaceutically acceptable salt thereof or a mixture thereof.

CLM What is claimed is:

11. The patch of claim 5, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:

. . . package of claim 12, wherein the local anesthetic comprises a sodium-channel blocker, an antidepressant, an NMDA receptor antagonist, or an opioid, or a pharmaceutically acceptable salt thereof or a mixture thereof.

CLM What is claimed is:

21. The package of claim 15, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:

. . . method of claim 22, wherein the local anesthetic comprises a sodium-channel blocker, an antidepressant, an NMDA receptor antagonist,

or an opioid, or a pharmaceutically acceptable salt thereof or a mixture thereof.

CLM What is claimed is:
32. The method of claim 26, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
. . . method of claim 33, wherein the local anesthetic comprises a sodium-channel blocker, an antidepressant, an NMDA receptor antagonist, or an opioid, or a pharmaceutically acceptable salt thereof or a mixture thereof.

CLM What is claimed is:
43. The method of claim 37, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
. . . hydrogel of claim 44, wherein the local anesthetic comprises a sodium-channel blocker, an antidepressant, an NMDA receptor antagonist, or an opioid, or a pharmaceutically acceptable salt thereof or a mixture thereof.

CLM What is claimed is:
53. The polyvinylpyrrolidone-based hydrogel of claim 47, wherein the opioid is morphine or a pharmaceutically acceptable salt thereof.

L9 ANSWER 33 OF 40 PHIN COPYRIGHT 2008 Informa UK Ltd on STN

ACCESSION NUMBER: 2002:9448 PHIN
DOCUMENT NUMBER: S00753734
DATA ENTRY DATE: 1 May 2002
TITLE: PUBLICATIONS - New from Scrip Reports - Osteoarthritis and Pain Management: Market Dynamics and Opportunities
SOURCE: Scrip-Online-plus (2002)
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL
TX In contrast with the COX-2 inhibitor market the opioid analgesic market has no new blockbuster drugs to boost its status. Instead, the market is supported by old drugs with. . . their use needs to be carefully monitored. The perceived dangerous side effects and fears of addiction and tolerance to strong opioid analgesics (eg morphine) have led to restrictions and controversy regarding their use. With changing attitudes towards the contribution of successful. . .

TX New developments in the opioid analgesic market are focused on the generation of novel and improved formulations of the established drugs, including combination formulations and. . .

TX The report looks at the current state of the market for osteoarthritis-related pain and pain management as a whole. It provides an overview of the mechanisms of pain and discusses some of the major chronic pain indications and their management. These include musculoskeletal pain (particularly osteoarthritis), cancer pain, neuropathic pain

(as seen in diabetic neuropathy) and post-operative pain . A brief overview of migraine is included but the report does not cover specific migraine drugs. Particular attention is given. . .

TX The . . . for the treatment of osteoarthritis and the major pain indications are reviewed in depth. These include NSAIDs, COX-2 inhibitors and opioid analgesics, and other classes of drugs also which are marketed for indications other than pain management but are used as. . .

TX A number of companies are investigating novel approaches to the treatment of osteoarthritis and the major pain indications. The report highlights some of these and provides tabulated summaries of the relevant drugs in clinical and preclinical development. Of particular importance are developments in the market for drugs to treat the poorly understood condition of neuropathic pain. Specific drug treatments for neuropathic pain do not exist and it represents a significant area of unmet medical need and a growing market opportunity.

TX

L9 ANSWER 34 OF 40 USPATFULL on STN DUPLICATE 5
ACCESSION NUMBER: 2002:141556 USPATFULL
TITLE: Method for treating tension-type headache
INVENTOR(S): Olesen, Jes, Hellerup, DENMARK

10574438

Bendtsen, Lars, Slagelse, DENMARK
Jensen, Rigmor, Virum, DENMARK
Madsen, Ulf, Horsholm, DENMARK

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20020072543	A1	20020613
	US 6649605	B2	20031118
APPLICATION INFO.:	US 2001-941855	A1	20010830 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-304115, filed on 4 May 1999, PATENTED Division of Ser. No. WO 1997-DK502, filed on 4 Nov 1997, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-85413P	19980514 (60)
	US 1996-30294P	19961105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BROWDY AND NEIMARK, P.L.L.C., 624 Ninth Street, N.W., Washington, DC, 20001
NUMBER OF CLAIMS: 142
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Page(s)
LINE COUNT: 5193
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Mirtazapine (10) or Venlafaxine (11); adamantanamines, such as Memantine (12); arylcyclohexylamines, such as Ketamine (13); arylcyclohexylamines, such as Norketamine (14), opioid derivatives, such Dextromethorphan (15); glycylamides, such as Remacemide (16); piperidinylethanols, such as Ifenprodil (17); piperidinylethanols, such as Eliprodil (18): diguanidines,. . .

DETD . . . Although initially employed in humans to control seizures, recent clinical cases indicated that the agent showed efficacy in treating human neuropathic pain states (Rosner et al 1996), and a considerably effect in several experimental pain models (Hwang and Yaksh 1996, Xiao and Bennett 1996). The exact mechanism is not fully understood, but several Mechanisms have. . .

DETD [0421] Hwang J, Yaksh T L. The effect of intrathecal gabapentin on tactile evoked allodynia in a surgically induced neuropathic pain model in the rat. Regional Anaest 1997, in press.

DETD . . . D J. The inhibition of nitric oxide-activated poly (ADP-ribose) synthase attenuates transsynaptic alteration of spinal cord dorsal horn neurons and neuropathic pain in the rat. Pain 1997;72:355-366.

DETD [0488] Rosner H, Rubin L, Kestenbaum A. Gabapentin, adjunctive therapy in neuropathic pain states. Clin J Pain 1996;12:56-58.

DETD [0511] Worz R, Lobisch M, Gessler M, Grotemeyer K H, Nehrfich D, May A, Schabet M, Schwittmann B. Flupirtine versus placebo in chronic tension-type headache. Headache Quaterly, 7(1):30-38.

DETD [0512] Xiao W H, Bennett G J. Gabapentin relieves abnormal pain sensations via spinal site of action in a rat model of painful peripheral neuropathy. Pain, in press.

CLM What is claimed is:

. . . to claim 43, wherein the agent is selected from a group consisting of polycyclic amines, tricyclic antidepressants, adamantanamines,

arylcyclohexylamines, arylcyclohexylamines, opioid derivatives, glycylamides, piperidinylethanols, piperidinylethanols, diguanidines, g-aminobutyric acid derivatives, polycyclic amines or derivatives of any of the above which are noncompetitive. . .

L9 ANSWER 35 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2001:148001 USPATFULL
TITLE:	Method for treating tension-type headache with inhibitors of nitric oxide and nitric oxide synthase
INVENTOR(S):	Olesen, Jes, Hellerup, Denmark Bendtsen, Lars, Slagelse, Denmark Jensen, Rigmor, Virum, Denmark Madsen, Ulf, Horsholm, Denmark
PATENT ASSIGNEE(S):	Head Explorer APS, Herlev, Denmark (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6284794	B1	20010904
APPLICATION INFO.:	US 1999-304115		19990504 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1997-DK502, filed on 4 Nov 1997		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-85413P	19980514 (60)
	US 1996-30294P	19961105 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Jarvis, William R. A.
LEGAL REPRESENTATIVE:	Cooper, Iver P.
NUMBER OF CLAIMS:	12
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	25 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT:	5056

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Mirtazapine (10) or Venlafaxine (11); adamantanamines, such as Memantine (12); aryleyclohexylamines, such as Ketamine (13), arylcyclohexylamines, such as Norketamine (14); opioid derivatives, such Dextromethorphan (15); glycylamides, such as Remacemide (16): piperidinylethanols, such as Ifenprodil (17); piperidinylethanols, such as Eliprodil (18); diguanidines,. . .

DETD . . . Although initially employed in humans to control seizures, recent clinical cases indicated that the agent showed efficacy in treating human neuropathic pain states (Rosner et al. 1996), and a considerably effect in several experimental pain models (Hwang and Yaksh 1996, Xiao and Bennett 1996). The exact mechanism is not full understood, but several mechanisms have. . .

DETD Hwang J, Yaksh T L. The effect of intrathecal gabapentin on tactile evoked allodynia in a surgically induced neuropathic pain model in the rat. Regional Anaest 1997, in press.

DETD . . . Mayer DJ. The inhibition of nitric oxide-activated poly (ADP-ribose) synthase attenuates transsynaptic alteration of spinal cord dorsal horn neurons and neuropathic pain in the rat. Pain 1997;72:355-366.

DETD Rosner H, Rubin L, Kestenbaurn A. Gabapentin, adjunctive therapy in

neuropathic pain states. Clin J Pain 1996;12:56-58.

DETD Worz R, Lobisch M, Gessler M, Grotemeyer K H, Nehrfich D, May A, Schabet M, Schwittmann B. Flupirtine versus placebo in chronic tension-type headache. Headache Quaterly, 7(1): 30-38.

DETD Xiao WH, Bennett G J. Gabapentin relieves abnormal pain sensations via spinal site of action in a rat model of painful peripheral neuropathy. Pain, in press.

L9 ANSWER 36 OF 40 PHIN COPYRIGHT 2008 Informa UK Ltd on STN

ACCESSION NUMBER: 2000:11197 PHIN
DOCUMENT NUMBER: S00668808
DATA ENTRY DATE: 15 Jun 2000
TITLE: PUBLICATIONS - New from Scrip Reports - Advanced Pain Management (February 2000)
SOURCE: Scrip-Online-plus (2000)
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

TX Conversely, the perceived dangerous side effects and fears of addiction and tolerance associated with strong opioid compounds (eg morphine) has lead to restrictions and controversy regarding their use. However, studies have demonstrated that the risks are. . . chronic pain of a non-malignant nature. When chronic pain patients complain that they envy cancer pain patients for the strong opioid treatment they receive, it is even clearer that misconceptions about these compounds must be dissolved if chronic pain management is. . .

TX Compounds in development for severe pain include treatment for 'breakthrough' cancer pain that affects 25% of cancer pain patients receiving round-the-clock opioid treatment. Actiq (fentanyl citrate) which is available in the US, may soon reach the UK as the first oral transmucosal. . . this indication and inhaled morphine compounds are also in development with the potential for outpatient use. As an alternative, severe pain sufferers can benefit from 72 hours of pain relief in the form of a convenient transdermal patch; opioids are also showing potential for treating neuropathic pain in both cancer and AIDS patients.

TX Other . . . of opioids whilst reducing inevitable tolerance to them; tachykinins (neurokinins) which affect the function of substance P, implicated in chronic pain and migraine; NMDA/non-NMDA-receptor antagonists; anticonvulsants such as pregabalin and topiramate for neuropathic pain and migraine prophylaxis; cannabinoids; vannilloids; the novel calcium channel antagonist, ziconotide, for neuropathic pain; delta opioid-receptor antagonists; bisphosphontes for bone pain due to osteoporosis and cancer metastases; and neurotoxins for migraine and chronic pain.

TX Preclinical research includes: tripeptides for neuropathic and post-operative pain; the potential to treat unresponsive chronic pain using injectable toxins attached to substance P to cause cell death in the neurons responsible for the pain; neural cell transplantation; antibody coupled immunotoxins; and sodium channel blockers, also potentially for neuropathic pain.

TX At . . . or serious surgery; chronic pain sufferers who want to return to work; AIDS patients; the terminally ill who may be opioid tolerant; drug addicts; and the elderly.

TX

L9 ANSWER 37 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2000:121543 USPATFULL
TITLE:	Use of retigabine for the treatment of neuropathic pain
INVENTOR(S):	Rundfeldt, Chris, Coswig, Germany, Federal Republic of Bartsch, Reni, Ottendorf-Okrilla, Germany, Federal Republic of Rostock, Angelika, Radebeul, Germany, Federal Republic of Tober, Christine, Weinbohla, Germany, Federal Republic of Dost, Rita, Dresden, Germany, Federal Republic of
PATENT ASSIGNEE(S):	ASTA Medica Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6117900		20000912	
APPLICATION INFO.:	US 1999-406135		19990927	(9)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			

PRIMARY EXAMINER: Spivack, Phyllis G.
LEGAL REPRESENTATIVE: Pillsbury Madison & Sutro LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Use of retigabine for the treatment of neuropathic pain

AB . . . to the use of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of formula I ##STR1## or its pharmaceutically utilizable salts, for the prophylaxis and treatment of neuropathic pain.

SUMM . . . of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene of the formula I ##STR2## (INN: retigabine) or its pharmaceutically utilizable salts for the prophylaxis and treatment of neuropathic pain.

SUMM Neuropathic pain such as allodynia and hyperalgesia describes a particular type of pain sensation which differs from the customary perception of painful stimuli. Patients who suffer from hyperalgesic pain feel painful stimuli more strongly than healthy people. The term allodynia describes the phenomenon of the perception of stimuli which are not painful per se, such as contact or heat/cold, as pain. In some cases, the perceptions felt are very strong and stressful. This modified pain sensation is covered in German and International usage by various terms which in some cases overlap in their meaning but. . . be used synonymously. In German usage, the terms Allodynie, Parasthesie, Hyperesthesie, Hyperalgesie and Phantomschmerz (allodynia, paraesthesia, hyperaesthesia hyperalgesia and phantom pain) are customary, in English usage, in addition to allodynia, hyperalgesia and phantom limb pain, the terms reflex sympathetic dystrophy (RSD) (Rogers and Valley, 1994) and sympathetically maintained pain (SMP) are furthermore used (Rogers J N; Valley M A, Reflex sympathetic dystrophy; Clin Podiatr Med Surg. January 1994; 11. . .

SUMM . . . unpleasant to painful perception of stimuli triggered by heat or by contact, which is based on a lowering of the pain threshold for these stimuli only. Hyperalgesia describes the excessive perception of stimuli of all sorts which are painful per se, again on account of a lowering of the pain threshold. Phantom pain is designated as the perception of pain which is non-existent, since, for example, the painful extremity has been amputated. In the scientific literature, this type of pain sensation is often subsumed under the term centrally mediated neuropathic pain. It is characteristic here that the actual pain sensation is not be attributed to a customary pain-inducing stimulus, but is generated by the peripheral or central nervous system, as the level or reaction of the pain -sensing and pain-transmitting system is altered. Unlike other forms of pain, neuropathic pain is usually chronic and customarily cannot be treated or can only be treated with difficulty with conventional analgesics such as. . .

SUMM 3. In the parts of the body affected, burn wounds lead to neuropathic hyperalgesias. Although the pain-inducing cause (heat) is no longer present, burn wounds are often extremely painful.

SUMM 4. After therapy with high doses of cytostatics for cancer treatment, patients often also report pain sensations (Brant 1998; Brant

J M, Cancer-related neuropathic pain. Nurse Pract. Forum. September 1998; 9 (3): 154-62). Tanner et al. (Tanner K D; Reichling D B; Levine J D, Nociceptor hyper-responsiveness during vincristine-induced painful peripheral neuropathy in the rat. J. Neurosci. Aug. 15, 1998; 18 (16): 6480-91) were able to show that pain which occurs in connection with vincristine treatment is caused by an increased stimulability of the peripheral pain receptors, that is by hyperalgesia.

SUMM 5. A tumour disorder itself can also elicit neuropathic pain (e.g. as a result of chronic nerve compression by the tumour) which belongs to the hyperalgesia type (Brant 1998; Brant J M, Cancer-related neuropathic pain. Nurse Pract. Forum, September 1998; 9 (3): 154-62).

SUMM . . . a widespread form of hyperalgesia which often occurs without visible damage to the nerves (Burchiel, 1993; Burchiel K J, Trigeminal neuropathic pain. Acta Neurochir. Suppl. Wien. 1993; 58; 145-9).

SUMM 10. In patients with chronic back pain, a compression of nerve roots of the spinal cord can often be observed. Apart from in chronic pain, this pressure damage to the nerve roots is also manifested in sensory malaises (paraesthesias). If the restriction is eliminated surgically, in spite of this a large proportion of the patients additionally complain about pain sensations. These persistent sensations are described as neuropathic pain and can be delimited diagnostically from other (inflammatory) forms of pain (Sorensen and Bengtsson, 1997; Sorensen J; Bengtsson M, Intravenous phentolamine test--an aid in the evaluation of patients with persistent pain after low-back surgery? Acta Anaesthesiol. Scand. May 1997; 41 (5): 581-5).

SUMM 11. In 10 to 20% of patients with spinal cord injuries, in some cases very severe pain sensations result which are generated in the brain for lack of intact spinal cord and are not to be related to a painful stimulus. This pain is described as central neuropathic pain (Eide 1998; Eide P K, Pathophysiological mechanisms of central neuropathic pain after spinal cord injury. Spinal cord. September 1998; 36 (9): 601-12).

SUMM 12. Pain occurring after amputations has characteristics of neuropathic pain (Hill 1999; Hill A, Phantom limb pain: a review of the literature on attributes and potential mechanisms. J. Pain Symptom Manage. February 1999; 17 (2): 125-42).

SUMM . . . of the participation of noradrenaline receptors, the transmitter substance of the sympathetic system, reference is also made to sympathetically maintained pain, since theses neurons are activated by physiological activation of the sympathetic system. In English usage, the term reflex sympathetic dystrophy. . . J N; Valley M A, Reflex sympathetic dystrophy; Clin. Podiatr. Med. Surg. January 1994; 11 (1): 73-83) or sympathetically maintained pain (SMP). Cytostatics such as vincristine lead directly to an increase in the excitability of peripheral pain receptors and in this way ought to induce hyperalgesia (Tanner et al. 1998; Tanner K D; Reichling D B; Levine J D, Nociceptor hyper-responsiveness during vincristine-induced painful peripheral neuropathy in the rat. J. Neurosci. Aug. 15, 1998; 18 (16); 6480-91).

SUMM . . . al., 1999; Pan H L; Eisenach J C; Chen S R, Gabapentine suppresses ectopic nerve discharges and reverses allodynia in

neuropathic rats. J Pharmacol Exp Ther. March 1999; 288 (3): 1026-30). By means of gabapentine, a medicament having a marked action in neuropathic pain, the spontaneous activity of these nerve cell foci (ectopic foci) can be suppressed in a dose-dependent manner. In the same. . . from the nerve stump beginning from day 4 for several weeks. This phenomenon is possibly to be related to phantom pain. Possibly, the spontaneous activity of these nerve fibres after amputation is to be attributed to a disinhibition of the NMDA. . . 211-20). Investigations in which it was possible to show that intrathecal administration of NMDA antagonists were able to reduce the pain also point to the involvement of the NMDA receptor. In summary, it can be established that overstimulation conditions of the involved nerves can play a role as a cause of the hyperalgesia or of the modified pain sensation, but the influence of further factors is probable.

SUMM In the therapy of these disorders, a completely clear differentiation must be made between the symptomatic treatment of the pain sensation and the nerve cell-protecting treatment of the causes of the disorder (Morz 1999, Morz R; Schmerzbehandlung bei diabetischen Neuropathien (Pain treatment in diabetic neuropathies), Fortschritte der Medizin 1999, 13: 29-30). In patients with diabetes-related neuropathic pain, the optimization of the metabolic levels to avoid further progression and the prevention of subsequent damage such as foot lesions is indicated as a basic programme, but this treatment has no effect on the pain symptoms per se.

SUMM . . . However, antidepressants such as amitriptyline, imipramine or paroxetine or anticonvulsants such as carbamazepine or gabapentine are employed. Tramadol, as an opioid analgesic, is also effective on account of its further actions on other receptors of the adrenergic system.

SUMM . . . literature, for example, the use of topiramate (U.S. Pat. No. 5,760,007) and moxonidine (EP 901 790) for the treatment of neuropathic pain is demonstrated.

SUMM The aim here is to treat the pain symptoms per se and not the causes. All medicaments mentioned, however, only lead to an alleviation of the pain symptoms in some of the patients. In herpes-induced neuropathic pain, it is possible prophylatically by the use of virostatics to protect the nerve cell causally from the harmful action of the virus at an early point in time of the disorder and thereby to reduce the expression of the neuropathic pain; these medicaments, however, are not effective symptomatically after the acute infection subsides. Affected patients can experience alleviation of the symptoms. . .

SUMM In compression-related neuropathic pain, it is possible to eliminate the primary cause of the disorder, for example, in the carpal tunnel syndrome or on. . . progression of the damage to the nerves. In spite of this, a high proportion of these patients still suffer from pain, which, in turn, does not respond well to classical analgesics, even a long time after the operation. Antidepressants and medicaments such as carbamazepine or gabapentine are used. In the case of amputation pain, the actual cause, the amputation, cannot be treated, so that neuropathic pain has to be treated only symptomatically with the abovementioned groups of medicaments. However, it has been attempted recently in the case of systematic amputations to counteract the development of neuropathic pain by conduction

blockade of the nerves to be severed for several days before carrying out the amputation. Although the first. . .

DETD In summary, it can be established that for the symptomatic treatment of neuropathic pain conventional analgesics have a low efficacy. Medicaments such as antidepressants, carbamazepine or valproate are used, which per se have no analgesic action on non-neuropathic forms of pain. The treatment of these patients, however, is often not satisfactory.

DETD There is therefore a great need for novel substances for the selective treatment of neuropathic forms of pain.

DETD The aim of this invention is to make available a substance with which the pain symptoms of neuropathic pain can be treated.

DETD Surprisingly, it has now been found that retigabine of the formula I ##STR3## has significant activities against neuropathic pain. Thus entirely new possibilities for the prophylaxis and treatment of neuropathic pain open up.

DETD Retigabine is a derivative of the non-opioid analgesic flupirtine, for which an anticonvulsive action was also demonstrated in addition to its analgesic action. By means of structural optimization with. . . modelling to separate the anticonvulsant from the analgesic action in this substance class. Retigabine has a stronger anticonvulsant action than flupirtine, but an analgesic action in models of acute pain is no longer detectable (Rostock et al., 1996; Rostock A; Tober. . .

DETD Unexpectedly, we were able to establish that retigabine has marked dose-dependent action against neuropathic pain. As expected, however, the analgesic action, as is seen in this model in the early phase, was only low and. . .

DETD Retigabine inhibited the late phase of the pain reactions, to be described as hyperalgesia or neuropathic pain, in a dose-dependent manner after 5, 10 and 20 mg/kg orally. The action of 10 mg/kg of retigabine corresponded approximately. . .

CLM What is claimed is:
2. The method of claim 1 wherein said pain is selected from the group consisting of neuropathic pain, allodynia, hyperalgesic pain and phantom pain.

CLM What is claimed is:
3. The method of claim 2 wherein said pain is neuropathic pain.

CLM What is claimed is:
4. The method of claim 3 wherein said pain is neuropathic pain in migraine.

CLM What is claimed is:
5. The method of claim 3 wherein said pain is neuropathic pain in diabetic neuropathy.

L9 ANSWER 38 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2000:15651 USPATFULL
TITLE: Use of substituted 2,4-imidazolidinedione compounds as analgesics
INVENTOR(S): Zimmer, Oswald, Wuerselen, Germany, Federal Republic of
Selve, Norma, Aachen, Germany, Federal Republic of

10574438

PATENT ASSIGNEE(S):	Gruenenthal GmbH, Aachen, Germany, Federal Republic of (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6022875		20000208
APPLICATION INFO.:	US 1998-126753		19980731 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	DE 1997-19732928		19970731
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Jarvis, William R. A.		
LEGAL REPRESENTATIVE:	Evenson, McKeown, Edwards & Lenahan, P.L.L.C.		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
LINE COUNT:	274		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Pain is a subjective sensory experience consisting of a sensory component and an affective component. The physiological aspects of the aetiology of pain comprise reception of any physical/chemical stimulus of a potentially tissue-threatening intensity by activation of the so-called nociceptors, specific uni- or polymodal nocisensors of high-threshold primary ascending neural pathways. When considering the pathophysiological aspects of the aetiology of pain, all the components of the nociceptive system may be altered: reception by nocisensors, transmission to the spinal level, perception, awareness. . . by disruption of the afferent system but also by disrupted perception and processing and disruption of the descending, controlling, endogenic pain-relieving system. In chronic or neuropathic pain, various phenomena occur including sensitisation of the nocisensors by endogenic or exogenic substances. In the event of persistent stimulation or. . .

SUMM . . . an analgesic. Particularly suitable further active substances are selected from at least one of the groups opioids, tramadol material and non-opioid analgesics. Examples of opioids include morphine, hydromorphone, codeine, oxycodone, dihydrocodeine, dextropropoxyphene, buprenorphine, levomethadone, fentanyl, sufentanil, together with the pharmaceutical salts. . . herein by reference, as well as the pharmaceutical salts of the aforementioned tramadol materials in racemic or enantiomeric form. Suitable non-opioid analgesics include, for example, acidic non-opioid carboxylic acids and carboxylic acid esters, such as salicylates, arylacetic acids and arylpropionic acids, for example acetylsalicylic acid, diclofenac, naproxen, ketoprofen and ibuprofen, acidic non-opioid heterocyclic keto-enol acids such as oxicams and pyrazolidinediones, for example piroxicam and tenoxicam, non-acidic, non-opioid anilines and pyrazolinones, for example paracetamol and metamizol, together with non-opioid pyridylcarbamates, for example flupirtine and benzoxazocines, for example nefopam.

SUMM . . . anti-nociceptive action of the substituted 2,4-imidazolidinedione compounds of the formula I cannot be explained by known anti-nociceptive mechanisms, such as μ- opioid receptor agonism, monoaminergic re-uptake inhibition or by interaction with a receptor such as adenosine, α/β-adrenoceptor, GABA, galanin, glutamate/NMDA, histamine, somatostatin,. . .

10574438

SUMM . . . 2,4-imidazolidinedione compounds of the formula I are preferably used for the production of pharmaceutical preparations for the treatment of chronic pain conditions. Chronic pain conditions, i.e. chronic inflammatory and chronic neuropathic pain conditions, occur, for example, in rheumatism, secondary inflammatory osteoarthrosis, back pain, tension headaches, trauma, herpes zoster and trigeminal neuralgia.

CLM What is claimed is:

. . . is administered in combination with at least one active substance selected from the group consisting of opioids, tramadol material and non-opioid analgesics.

L9 ANSWER 39 OF 40 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999242458 EMBASE

TITLE: [Post-traumatic pain. Causes and therapeutic concepts]. Posttraumatische schmerzen. Ursachen und therapiemoglichkeiten.

AUTHOR: Dertwinkel, R., Dr. (correspondence)

CORPORATE SOURCE: Klinik fur Anasthesiologie, Intensiv- und Schmerztherapie, Burkle-de-la-Camp-Platz 1, D-44789 Bochum, Germany.

AUTHOR: Zenz, M.; Donner, B.; Wiebalck, A.; Strumpf, M.

SOURCE: Orthopade, (Jun 1999) Vol. 28, No. 6, pp. 509-517.
Refs: 21
ISSN: 0085-4530 CODEN: ORHPBG

COUNTRY: Germany

DOCUMENT TYPE: Journal; General Review; (Review)

FILE SEGMENT: 019 Rehabilitation and Physical Medicine
024 Anesthesiology
033 Orthopedic Surgery
037 Drug Literature Index

LANGUAGE: German

SUMMARY LANGUAGE: English; German

ENTRY DATE: Entered STN: 2 Aug 1999
Last Updated on STN: 2 Aug 1999

AB . . . most posttraumatic pain situations peripheral nociceptors are activated and normal afferences are conducted via an intact nociceptive system. In contrast, neuropathic pain is caused by lesions of the nervous system itself. Mechanisms of central sensibilization and involvement of the sympathetic nervous system may lead to chronification of such pain conditions. The therapeutic regime of nociceptive and neuropathic pain is demonstrated by algorithms of treatment modalities. Apart from classic non-opioid analgesics, co-analgesics and opioids have an important status in chronic pain management as well. Prescription of these substances has to. . .

CT Medical Descriptors:
adrenergic system
*chronic pain
human
*injury
nerve stimulation
neuropathy
nociception
physiotherapy
review

sympathetic blocking
amitriptyline
*analgesic agent
anticonvulsive agent
*antipyretic analgesic agent
*antirheumatic agent
buprenorphine
carbamazepine
diclofenac
dihydrocodeine
dipyrone
doxepin
flupirtine
gabapentin
ibuprofen
meloxicam
morphine
naloxone
naproxen
*nonsteroid antiinflammatory agent
*opiate
oxycodone
paracetamol
tilidine
tramadol
*tricyclic antidepressant agent
RN. . . (buprenorphine) 52485-79-7, 53152-21-9; (carbamazepine) 298-46-4, 8047-84-5; (diclofenac) 15307-79-6, 15307-86-5; (dihydrocodeine) 125-28-0, 24204-13-5, 5965-13-9; (dipyrone) 50567-35-6, 5907-38-0, 68-89-3; (doxepin) 1229-29-4, 1668-19-5; (flupirtine) 56995-20-1 ; (gabapentin) 60142-96-3; (ibuprofen) 15687-27-1; (meloxicam) 71125-38-7; (morphine) 52-26-6, 57-27-2; (naloxone) 357-08-4, 465-65-6; (naproxen) 22204-53-1, 26159-34-2; (opiate) 53663-61-9, 8002-76-4, 8008-60-4; (oxycodone). . .

L9 ANSWER 40 OF 40 EMBASE
ACCESSION NUMBER: 1998101529 EMBASE
TITLE: [Non-opioid-analgesics and co-analgesics in the treatment of chronic pain].
Nicht-Opioidanalgetika und Co-Analgetika in der Therapie chronischer Schmerzen.
AUTHOR: Gehling, Markus, Dr. (correspondence); Niebergall, Henner
CORPORATE SOURCE: Klin. F. Anasthesiologie, I., Stadtische Kliniken Kassel gGmbH, Anaesthiol. Univ. Klin. Freiburg.
AUTHOR: Gehling, Markus, Dr. (correspondence)
CORPORATE SOURCE: Klin. F. Anasthesiologie, I., Stadtische Kliniken Kassel gGmbH, Monchebergstr, 41-43, 34125 Kassel, Germany.
AUTHOR: Gehling, Markus, Dr. (correspondence)
CORPORATE SOURCE: Klinik fur Anasthesiologie, Intensivmedizin, und Schmerztherapie, Stadtische Kliniken Kassen gGmbH, Monchebergstr 41-43, 34125 Kassel, Germany.
SOURCE: Zeitschrift fur Arztliche Fortbildung und Qualitatssicherung, (Jan 1998) Vol. 92, No. 1, pp. 41-46.
Refs: 20
ISSN: 1431-7621 CODEN: ZAFQFF
COUNTRY: Germany

10574438

DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
008 Neurology and Neurosurgery
LANGUAGE: German
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 2 Jun 1998
Last Updated on STN: 2 Jun 1998

TI [Non-opioid-analgesics and co-analgesics in the treatment of chronic pain].
Nicht-Opioidanalgetika und Co-Analgetika in der Therapie chronischer Schmerzen.

AB Efficacy and side effects of non-opioid-analgesics were analysed in a standardized review of placebo-controlled or double-blind studies. In rheumatoid arthritis, ibuprofen showed the best ratio of. . . pain, ibuprofen is the treatment of the first choice followed by naproxen and diclofenac. No sufficient data on non-opioids in neuropathic pain were available. The dose administered in the management of chronic pain should be low in order to reduce the incidence. . . 7,4%, meloxicam 13,0% and diclofenac 17,8%. Since differences in efficacy were not clinically relevant, the indication for a special non- opioid -analgesic medication should focus on the prevention of side-effects.

CT Medical Descriptors:
*bone . . .
therapy
diflunisal: AE, adverse drug reaction
diflunisal: DO, drug dose
diflunisal: DT, drug therapy
dipyrone: AE, adverse drug reaction
dipyrone: DO, drug dose
dipyrone: DT, drug therapy
flupirtine: AE, adverse drug reaction
flupirtine: DO, drug dose
flupirtine: DT, drug therapy
flurbiprofen: AE, adverse drug reaction
flurbiprofen: DO, drug dose
flurbiprofen: DT, drug therapy
ibuprofen: AE, adverse drug reaction
ibuprofen: DO, drug dose
ibuprofen:. . .

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (diclofenac) 15307-79-6, 15307-86-5; (diflunisal) 22494-42-4; (dipyrone) 50567-35-6, 5907-38-0, 68-89-3; (flupirtine) 56995-20-1; (flurbiprofen) 5104-49-4; (ibuprofen) 15687-27-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (meloxicam) 71125-38-7; (naproxen) 22204-53-1, 26159-34-2; (nefopam) 13669-70-0, 23327-57-3; (paracetamol) 103-90-2; (phenylbutazone) 129-18-0,. . .

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	84.56	93.51

FILE 'STNGUIDE' ENTERED AT 16:13:29 ON 03 SEP 2008

Jagoe

10574438

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Aug 29, 2008 (20080829/UP).

=> d his

     (FILE 'HOME' ENTERED AT 16:00:08 ON 03 SEP 2008)

     FILE 'REGISTRY' ENTERED AT 16:00:22 ON 03 SEP 2008
L1   STRUCTURE UPLOADED
L2   0 S L1

     FILE 'HOME' ENTERED AT 16:01:31 ON 03 SEP 2008

     FILE 'REGISTRY' ENTERED AT 16:02:08 ON 03 SEP 2008
L3   1 S FLUPIRTINE/CN

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CAPLUS, DISSABS,
     DRUGMONOG2, EMBAL, EMBASE, IFIPAT, IMSDRUGNEWS, IMSPRODUCT, IPA, LIFESCI,
     MEDLINE, NAPRALERT, NLDB, PHIC, PHIN, SCISEARCH, TOXCENTER, USPATFULL,
     USPATOLD, USPAT2' ENTERED AT 16:02:45 ON 03 SEP 2008
L4   1879 S L3 OR FLUPIRTINE
L5   59357 S NEUROPATH? (S) PAIN
L6   101 S L4 AND L5
L7   274294 S OPIOID
L8   47 S L6 AND L7
L9   40 DUP REM L8 (7 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 16:13:29 ON 03 SEP 2008

=> d l9 1-10 ibib, kwic
YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS, EMBASE, IFIPAT, IMSDRUGNEWS, LIFESCI,
PHIN, SCISEARCH, USPATFULL' - CONTINUE? (Y)/N:y

L9   ANSWER 1 OF 40 IFIPAT COPYRIGHT 2008 IFI on STN
AN   11699453 IFIPAT;IFIUDB;IFICDB
TITLE: METHODS AND COMPOSITIONS
INVENTOR(S):   Goodchild; Colin, Malvern, AU
                          Nadeson; Raymond, Lethbridge, AU
                          Tucker; Adam Paul, Hawthorn, AU
PATENT ASSIGNEE(S):   CNSBio Pty Ltd, Melbourne, AU
AGENT: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH
                          AVE, SUITE 5400, SEATTLE, WA, 98104, US

                             NUMBER   PK   DATE
                          ----------------- -- --------
PATENT INFORMATION: US 20080039463   A1 20080214
APPLICATION INFORMATION: US 2004-574438   20041216
                          WO 2004-AU1772   20041216
                                                 20070625 PCT 371 date
                                                 20070625 PCT 102(e) date

Jagoe

	NUMBER	DATE
PRIORITY APPLN. INFO.:	AU 2003-906981	20031216
FAMILY INFORMATION:	US 20080039463	20080214

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION
ENTRY DATE: Entered STN: 15 Feb 2008
Last Updated on STN: 14 Mar 2008

NUMBER OF CLAIMS: 6

AB Compositions of flupirtine for management of neuropathic or inflammatory pain optionally including one or more other analgesics including opiates, NSAIDS and other active agents in immediate and controlled release forms.. . .

ACLM 44. The method of claim 43 further comprising the administration of the opioid concurrently or sequentially to the flupirtine.
45. The method of claim 44 wherein the opioid is morphine, fentanyl, oxycodone or a pharmaceutically acceptable salt thereof.
46. The method of any one of claims 43 to 45 wherein the opioid does not induce overt sedation in the presence of flupirtine.
47. The method of claim 43 wherein flupirtine is administered in an amount of about 0.5 mg/kg to about 20 mg/kg of body weight.

ECLM 1.-42. (canceled)
43. A method for inducing an analgesic response to neuropathic pain in a mammal, said method comprising administering to the mammal, a composition comprising the structure or a pharmaceutically acceptable salt thereof in combination with an opioid selected from the list consisting of fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene,. . . homologs or analogs thereof, in an amount effective to reduce the level of or to otherwise ameliorate the sensation of pain.

L9 ANSWER 2 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2008:238980 USPATFULL
TITLE: (S)-N-Stereoisomers of 7,8-Saturated-4,5-Epoxy-Morphinanium Analogs
INVENTOR(S): Perez, Julio, Tarrytown, NY, UNITED STATES
Han, Amy Qi, Hockessin, DE, UNITED STATES
Rotshteyn, Yakov, Monroe, NY, UNITED STATES
PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., Tarrytown, NY, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080207669	A1	20080828
APPLICATION INFO.:	US 2007-944242	A1	20071121 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-867101P	20061122 (60)
	US 2006-867394P	20061127 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KELLEY DRYE & WARREN LLP, 400 ALTLANTIC STREET , 13TH

FLOOR, STAMFORD, CT, 06901, US
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 4224

SUMM . . . (although very low) with very substantial antagonist activity in comparison (to its agonist activity) whereas the equatorial N-substituent displayed pure opioid antagonist activity.

SUMM . . . spatial location of "antagonist substituents" such as N-allyl and cyclopropylmethyl, determine the "purity" of the antagonistic pharmacological properties of an opioid drug. Feinberg et al. theorize that a 14-hydroxyl group on the morphinan structure helps to increase the proportion of antagonistic. . .

SUMM . . . also provided. A protocol for obtaining (S)-7,8-saturated-4,5-epoxy-morphinaniums is also provided. In addition, it has been discovered, surprisingly, that (S)-7,8-saturated-4,5-epoxy-morphinaniums have opioid agonist activity. The invention provides synthetic routes for stereoselective synthesis of (S)-7,8-saturated-4,5-epoxy-morphinaniums, substantially pure (S)-7,8-saturated-4,5-epoxy-morphinaniums, crystals of substantially pure (S)-7,8-saturated-4,5-epoxy-morphinaniums,. . .

SUMM . . . the pharmaceutical preparation further includes a therapeutic agent other than the 7,8-saturated-4,5-epoxy-morphinanium. In one embodiment, the therapeutic agent is an opioid or opioid agonist. Examples of opioids or opioid agonists are alfentanil, anileridine, asunadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), saturatedcodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan,. . . nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, tramadol, or combinations thereof. In some embodiments, the opioid or opioid agonist does not readily cross the blood brain barrier and, therefore, has substantially no central nervous system (CNS) activity when. . .

SUMM In other embodiments the therapeutic agent is an opioid antagonist. Opioid antagonists include peripheral mu opioid antagonists. Examples of peripheral mu opioid antagonists include quaternary derivatives of noroxymorphone (See Goldberg et al, U.S. Pat. No. 4,176,186, and Cantrell et al WO 2004/043964),. . . and 6,469,030, quaternary benzomorphan compounds such as described in U.S. Pat. Nos. 3,723,440 and 6,469,030. In one embodiment, the peripheral opioid antagonist is an (S)-7,8-saturated-4,5-epoxy-morphinanium.

SUMM In other embodiments, the therapeutic agent is not an opioid, opioid agonist, or an opioid antagonist. For example, the therapeutic agent can be an antiviral agent, antibiotic agent, antifungal agent, antibacterial agent, antiseptic agent, anti-protozoal. . .

SUMM . . . in time whereby both agents are treating the condition at the same time. In one embodiment, the agent is an opioid or an opioid agonist. In another embodiment, the agent is not an opioid or an opioid agonist.

SUMM . . . administered in conjunction with another motility inhibiting agent that is not a (S)-7,8-saturated-4,5-epoxy-morphinanium. In one embodiment, the agent is an opioid or an opioid agonist. Opioids and opioid agonists are described above. In

another embodiment, the agent is not an opioid or an opioid agonist. Examples of such gastrointestinal motility inhibiting agents are described below, each as if recited specifically in this summary of. . .

SUMM . . . administering to the subject a therapeutic agent other than (S)-7,8-saturated-4,5-epoxy-morphinanium. In one embodiment, the agent other than (S)-7,8-saturated-4,5-epoxy-morphinanium is an opioid . In another embodiment, the agent other than (S)-7,8-saturated-4,5-epoxy-morphinanium is a nonopioid pain relieving agent. Nonopioid pain relieving agents include corticosteroids. . .

SUMM . . . patient in need of such treatment a pharmaceutical composition containing an (S)-7,8-saturated-4,5-epoxy-morphinanium and administering to the subject a peripheral mu opioid antagonist, both in amounts to regulate gastrointestinal function. In one embodiment, the peripheral mu opioid antagonist is an (R)-7,8-saturated-4,5-epoxy-morphinanium.

SUMM . . . include a therapeutic agent other than an (S)-7,8-saturated-4,5-epoxy-morphinanium. The therapeutic agent other than the (S)-7,8-saturated-4,5-epoxy-morphinanium in one embodiment is an opioid or opioid agonist. In one aspect, the opioid or opioid agonist has substantially no CNS activity when administered systemically (i.e., is "peripherally acting"). In other embodiments, the therapeutic agent other than the (S)-7,8-saturated-4,5-epoxy-morphinanium is an opioid antagonist. Opioid antagonists include peripheral mu opioid antagonists. In one embodiment, the peripheral opioid antagonist is an (R)-7,8-saturated-4,5-epoxy-morphinanium. In other embodiments, the agent other than the (S)-7,8-saturated-4,5-epoxy-morphinanium is an antiviral agent, antibiotic agent, antifungal. . .

SUMM According to another embodiment of the invention, methods are provided for ensuring the manufacture of (S)-7,8-saturated-4,5-epoxy-morphinanium (which is an opioid agonist) that is free of (R)-7,8-saturated-4,5-epoxy-morphinanium (which is an opioid antagonist). The methods permit for the first time the assurance that a pharmaceutical preparation of the (S)-7,8-saturated-4,5-epoxy-morphinaniums of the present. . .

DETD . . . also differ from one (R)-7,8-saturated-4,5-epoxy-morphinanium or mixtures of the (R)-7,8-saturated-4,5-epoxy-morphinanium and (S)-7,8-saturated-4,5-epoxy-morphinanium. Pure (S)-7,8-saturated-4,5-epoxy-morphinaniums may behave as agonists of peripheral opioid receptors as, for example, inhibiting gastrointestinal transit. As a consequence, (S)-7,8-saturated-4,5-epoxy-morphinanium activity may be interfered with or antagonized by (R)-7,8-saturated-4,5-epoxy-morphinanium. . .

DETD . . . particularly useful in reverse phase HPLC chromatography. The (S)-7,8-saturated-4,5-epoxy-morphinanium of the present invention by virtue of its agonist activity on opioid receptors, is useful as a standard of agonist activity in in vitro and in vivo opioid receptor assays such as those described herein.

DETD The (S)-7,8-saturated-4,5-epoxy-morphinaniums of the present invention can be used to regulate a condition mediated by one or more peripheral opioid receptors, prophylactically or therapeutically, to agonize peripheral opioid receptors, in particular peripheral mu opioid receptors. The subjects being administered an (S)-7,8-saturated-4,5-epoxy-morphinanium may receive treatment acutely, chronically or on an as needed basis.

DETD Mu and other opioid receptors exist in the gastrointestinal tract. Of the major classes of opioid receptors in the GI tract, mu receptors are principally involved in modulation of GI activity. Kappa opioid receptors may also play a role (Manara L et al Ann. Rev. Phamacol. Toxicol, 1985, 25:249-73). In general, the (S)-7,8-saturated-4,5-epoxy-morphinanium is used to prevent or treat conditions associated with the need for activation or modulation of opioid receptors, in particular, peripheral opioid receptors. Of interest is the use of (S)-7,8-saturated-4,5-epoxy-morphinaniums to prevent or treat conditions associated with the need for activation or modulation of opioid receptors in the GI tract, in particular mu opioid receptors. Such conditions which may be prevented or treated include diarrhea and used to prevent or inhibit certain forms of. . .

DETD . . . present invention can be used to treat diarrhea. Gastrointestinal function is regulated, at least in part, by one or more opioid receptors as well as endogenous opioids. Opioid antagonists are known to increase gastrointestinal motility and may thus be used effectively as a treatment for constipation. Opioid agonists on the other hand, in particular peripheral opioid agonists such as loperamide are known to decrease gastrointestinal motility and can be useful in treating diarrhea in mammals. Agonist (S)-7,8-saturated-4,5-epoxy-morphinaniums of the present invention, as an opioid agonist, can be administered to a patient in need of treatment for diarrhea. Diarrhea as used herein is defined as. . .

DETD The (S)-7,8-saturated-4,5-epoxy-morphinaniums of the present invention by virtue of their opioid agonist activity is useful in the prevention and treatment of diarrhea having diverse etiology including acute and chronic forms of. . .

DETD . . . administered in conjunction with another motility inhibiting agent that is not an (S)-7,8-saturated-4,5-epoxy-morphinanium. In one embodiment, the agent is an opioid or an opioid agonist. Opioids and opioid agonists are described above. In another embodiment, the agent is not an opioid or an opioid agonist. Examples of such nonopioid gastrointestinal motility inhibiting agents include, for example, cisapride, antacids, aluminum hydroxide, magnesium aluminum silicate, magnesium. . .

DETD . . . animal's response to a strong stimulus without obtunding general behavior or motor function are referred to as analgesics. Opiates and opioid agonists affect pain via interaction with specific opioid receptors. An (S)-7,8-saturated-4,5-epoxy-morphinanium of the present invention, in having agonist activity, may find use in the treatment of pain.

DETD In general, pain can be nociceptive, somatogenic, neurogenic, or psychogenic. Somatogenic pain can be muscular or skeletal (i.e., osteoarthritis, lumbosacral back pain, posttraumatic, myofascial), visceral (i.e., pancreatitis, ulcer, irritable bowel), ischemic (i.e., arteriosclerosis obliterans), or related to the progression of cancer (e.g., malignant or non-malignant). Neurogenic pain can be due to posttraumatic and postoperative neuralgia, can be related to neuropathies (i.e., diabetes, toxicity, etc.), and can be related to nerve entrapment, facial neuralgia, perineal neuralgia, postamputation, thalamic, causalgia, and reflex. . .

DETD Specific examples of conditions, diseases, disorders, and origins of pain amenable to management according to the present invention include, but are not necessarily limited to, cancer pain

(e.g., metastasis or non-metastatic cancer), inflammatory disease pain, neuropathic pain, postoperative pain, iatrogenic pain (e.g., pain following invasive procedures or high dose radiation therapy, e.g., involving scar tissue formation resulting in a debilitating compromise of freedom of motion and substantial pain), complex regional pain syndromes, failed-back pain (e.g., acute or chronic back pain), soft tissue pain, joints and bone pain , central pain, injury (e.g., debilitating injuries, e.g., paraplegia, quadriplegia, etc., as well as non-debilitating injury (e.g., to back, neck, spine, joints, legs, arms, hands, feet, etc.)), arthritic pain (e.g., rheumatoid arthritis, osteoarthritis, arthritic symptoms of unknown etiology, etc.), hereditary disease (e.g., sickle cell anemia), infectious disease and resulting. . . syndromes (e.g., Lyme disease, AIDS, etc.), headaches (e.g., migraines), causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, denervation, and the like. Pain can be associated with any portion(s) of the body, e.g., the musculoskeletal system, visceral organs, skin, nervous system, etc.

DETD The methods of the invention can be used to manage pain in patients who are opioid naive or who are no longer opioid naive. Exemplary opioid naive patients are those who have not received long-term opioid therapy for pain management. Exemplary non-opioid naive patients are those who have received short-term or long-term opioid therapy and have developed tolerance, dependence, or other undesirable side effect. For example, patients who have intractable adverse side effects with oral, intravenous, or intrathecal morphine, transdermal fentanyl patches, or conventionally administered subcutaneous infusions of fentanyl, morphine or other opioid can achieve good analgesia and maintain favorable side-effects profiles with delivery of an (S)-7,8-saturated-4,5-epoxy-morphinanium and derivatives thereof.

DETD . . . including but not limited, therapeutic agents that arc pain relieving agents. In one embodiment, the pain relieving agent is an opioid or opioid agonist. In another embodiment, the pain relieving agent is a nonopioid pain relieving agent such as a corticosteroid or a. . . Drinidene; Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone; Fluradoline Hydrochloride; Flurbiprofen; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride;. . .

DETD . . . production and it is believed that a decrease in TNF production will result in a reduction in inflammation. Peripherally acting opioid agonists have been shown to decrease TNF production (U.S. Pat. No. 6,190,691). The peripherally selective k-opioid, asimadoline, has been shown to be a potent anti-arthritic agent in an adjuvant-induced arthritis animal model (Binder, W. and Walker, J. S. Br. J. Pharma 124:647-654). Thus the peripheral opioid agonist activity of the (S)-7,8-saturated-4,5-epoxy-morphinanium and derivatives thereof provide for prevention and treatment of inflammatory conditions. While not being bound. . .

DETD . . . treatment protocol together with an (S)-7,8-saturated-4,5-epoxy-morphinanium are opioids. Use of an (S)-7,8-saturated-4,5-epoxy-morphinanium of the present invention, in combination with the

opioid, may result in an enhanced and apparently synergistic inhibition of gastrointestinal transit. Thus, the present invention provides pharmaceutical compositions comprising. . . in combination with one or more opioids. This will permit alteration of doses. For example, where a lower dose of opioid is desirable in treating certain peripherally mediated conditions, such may be reached by combination with an (S)-7,8-saturated-4,5-epoxy-morphinanium treatment.

DETD The opioid can be any pharmaceutically acceptable opioid. Common opioids are those selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin),. . .

DETD Depending on the desired effect to be achieved the opioid may be administered parenterally or other systemic route to affect both the central nervous system (CNS) and peripheral opioid receptors. The desired effect of the opioid in combination with an (S)-7,8-saturated-4,5-epoxy-morphinanium of the present invention may be prevention or treatment of diarrhea, prevention or treatment of. . . treatment of peripheral hyperalgesia. When the indication is prevention or treatment of peripheral hyperalgesia, it is desirable to provide an opioid which does not have concomitant CNS effects or alternatively to administer the opioid topically or locally such that the opioid does not substantially cross the blood brain barrier but provide an effect on peripheral opioid receptors.

DETD . . . e.g., U.S. Pat. No. 4,430,327; Burkhart et al. (1982) Peptides 3-869-871; Frederickson et al. (1991) Science 211:603-605] and other synthetic opioid peptides, such as H-Ty(R)-D-Nva-Phe-Orn-NH.sub.2, H-Ty(R)-D-Nle-Phe-Orn-NH.sub.2, H-Ty(R)-D-Arg-Phe-A.sub.2bu-NH.sub.2, H-Ty(R)-D-Arg-Phe-Ly(S)-NH.sub.2, and H-Ly(S)-Ty(R)-D-Arg-Phe-Ly(S)-NH.sub.2 [see, U.S. Pat. No. 5,312,899; see, also Gesellchen et al. (1981). . .

DETD . . . can be configured as an oral dosage. The oral dosage may be a liquid, a semisolid or a solid. An opioid may optionally be included in the oral dosage. The oral dosage may be configured to release the therapeutic agent(s) of the invention before, after or simultaneously with the other agent (and/or the opioid). The oral dosage may be configured to have the therapeutic agent(s) of the invention and the other agents release completely. . .

DETD . . . al PNAS USA 92(15):1431-1437; Wang, J B 1994, FEBS Lett 338:217-222). For example, a membrane may be associated with human opioid receptor material. Diprenorphine which has an affinity for all four opioid receptors, can be used as a competitive challenge to the test compound. Membranes can then be separated, and the binding. . .

DETD . . . μM) and GR113808 (0.1 μM) may be also present throughout an experiment to prevent prostanoid release and to block the k-opioid, 5-HT2, 5-HT3 and 5-HT4 receptors, respectively. The tissues in such tests are typically connected to force transducers for isometric tension. . .

DETD

Effects of (S)-17-(3'-phenylbut-2'ynyl)-4.5α-epoxy-3,14-di-hydroxy-17-methyl-6-oxomorphinanium iodide ("(S)-PM")
and (S)-17-(3,3-dimethylallyl)-4,5α-epoxy-3,14-di-hydroxy-17-methyl-6-oxomorphinanium iodide ("(S)-DMAM")
evaluated for agonist and antagonist activities at the μ- opioid

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receptors in the guinea pig ileum

Evaluation of agonist activity
Control
+
response to Responses to increasing concentrations of the compounds. . .
DETD

EC.sub.50 and IC.sub.50 values determined for (S)-17-(3'-phenylbut-2'ynyl)-4.5α-epoxy-3,14-di-hydroxy-17-methyl-6-oxomorphinanium iodide ("(S)-PM") and (S)-17-(3,3-dimethylallyl-dihydroxy-17-methyl-6-oxomorphinanium oxide ("(S)-DMAM") at theμ- opioid receptors in the guinea pig ileum

Compound	Agonist activity EC.sub.50 value	Antagonist activity IC.sub.50 value
(S)-PM	6.8.0E-06 M	No antagonist activity

. . .
DETD In Vitro Pharmacology cAMP Assay in CHO Cells Expressing Human mu, MOP) Receptor. The mu opioid receptor is G.sub.i coupled, which works by inhibiting a cAMP increase. Thus, changes in cAMP can be used to determine. . .
CLM What is claimed is:
26. The pharmaceutical composition of claim 25, wherein the therapeutic agent is an opioid agonist.

CLM What is claimed is:
27. The pharmaceutical composition of claim 26, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), saturatedcodeine, diphenoxylate, fedotozine,. . .
CLM What is claimed is:
28. The pharmaceutical composition of claim 26, wherein the opioid or opioid agonist has substantially no central nervous system (CNS) activity.

CLM What is claimed is:
29. The pharmaceutical composition of claim 25, wherein the therapeutic agent is not an opioid, opioid agonist or an opioid antagonist.

CLM What is claimed is:
30. The pharmaceutical composition of claim 29, wherein the therapeutic agent is an non-opioid analgesic/anti-oyretic, antiviral agent, an antibiotic agent, an antifungal agent, antibacterial agent, antiseptic agent, anti-protozoal agent, anti-parasitic agent, an anti-inflammatory agent,. . .
CLM What is claimed is:
. . . of claim 37, wherein the anti-diarrhea agent that is not the (S)-N-stereoisomer of the compound of claim 2 is an opioid or an opioid agonist.

CLM What is claimed is:
42. The method of claim 41 further comprising administering to the subject an opioid or an opioid agonist.

Jagoe

CLM What is claimed is:
. . . claim 45, wherein the therapeutic agent other than (S)-N-stereoisomer of the compound of claim 2 in the composition is an opioid.

CLM What is claimed is:
. . . to claim 58, further comprising a combination of compatible therapeutic agents wherein one of the therapeutic agents is a peripheral opioid antagonist.

CLM What is claimed is:
60. The method of claim 17, wherein the peripheral opioid antagonist is the counterpart (R)-N-stereoisomer of the compound.

L9 ANSWER 3 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2008:66442 USPATFULL
TITLE: Novel pharmaceutical compositions for treating chronic pain and pain associated with neuropathy
INVENTOR(S): Singh, Chandra Ulagaraj, San Antonio, TX, UNITED STATES
Woody, David Lloyd, New Braunfels, TX, UNITED STATES
Nulu, Jagaveerabhadra Rao, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080058362	A1	20080306
APPLICATION INFO.:	US 2007-892422	A1	20070822 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-841225P	20060831 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: NATHANIEL GORDON-CLARK, 1025 NORTH CALVERT STREET, BALTIMORE, MD, 21202, US
NUMBER OF CLAIMS: 57
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3156
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Novel pharmaceutical compositions for treating chronic pain and pain associated with neuropathy
SUMM Chronic pain can be somatogenic, neurogenic, or psychogenic in origin. Somatogenic pain can be muscular or skeletal. For example, osteoarthritis, lumbosacral back pain, posttraumatic, spinal and peripheral nervous system injury, phantom pains due to amputations and avulsions and myofascial pain are unfortunately familiar to many of us. Maladies of the viscera such as chronic pancreatitis, ulcers, and irritable bowel disease give rise to pain in large numbers of people. Ischemic events frequently cause pain as in arteriosclerosis obliterans, stroke, heart attack, and angina pectoris. Cancer is also the cause of significant pain in our society. Neurogenic pain can be due to posttraumatic and postoperative neuralgia. Neurogenic pain also can be related to degenerative neuropathies due to diabetes and can be secondary to a variety of toxic insults. Neurogenic

pain can also be due to nerve entrapment, irritation or disruption, facial neuralgia, perineal neuralgia, post-amputation phantom pain, thalamic, causalgia, and reflex sympathetic dystrophy. Psychogenic pain on the other hand, is not amenable to corrective physical treatments or to pharmacological treatments that either alleviate some attribute of a pathophysiologic process. Psychogenic pain is treated instead with psychiatric interventions such as counseling and psychopharmaceuticals such as antidepressants.

SUMM Neuropathic pain is a common variety of chronic pain. It can be defined as pain that results from an abnormal functioning of the peripheral and/or central nervous system. A critical component of this abnormal functioning is an exaggerated response of pain related nerve cells either in the periphery or in the central nervous system. An example is the pain known as causalgia, wherein even a light touch to the skin is felt as an excruciating burning pain. Neuropathic pain is thought to be a consequence of damage to peripheral nerves or to regions of the central nervous system. However, abnormal functioning of pain related regions of the nervous system can also occur with chronic inflammatory conditions such as certain types of arthritis and metabolic disorders such as diabetes. Thus, many types of chronic pain related to inflammatory processes can be considered to be at least partly neuropathic pains.

SUMM Other treatments include the use of antidepressants, specifically, the tricyclic antidepressants (TCA's), such as amytriptiline. These relieve pain by altering levels of serotonin in the body. The antineuralgic properties of TCA's were shown to be independent from their. . . used. In general, the SSRI's have not been found to be as effective as the TCA's for the treatment of neuropathic pain, but are better tolerated. The side effects of the SSRI's include sweating, stomach upset, somnolence, dizziness, decreased libido, and ejaculatory. . .

SUMM Other approaches to the treatment of chronic pain and neuropathic pain have included the administration of a pharmaceutically acceptable acid addition salt or a protonated derivative of at least one microtubule. . . U.S. Pat. No. 4,602,909, (3S,4S)-7-hydroxy-Δ.sup.6-tetrahydro-cannabinol homologues and derivatives essentially free of the (3R,4R) form as disclosed in Hayes et al, Pain, 48 (1992) 391-396, Mao et al, Brain Res., 584 (1992) 18-27, 584 (1992) 28-35 and 588 (1992) 144-149 and the. . .

SUMM . . . Rains and Bryson, 1995). Topical capsaicin produces benefit in postherpetic neuralgia (Bernstein et al, 1989; Watson et al, 1993), diabetic neuropathy (Capsaicin Study Group, 1992), postmastectomy pain syndrome (Watson and Evans, 1992; Dini et al, 1993), oral neuropathic pain, trigeminal neuralgia, and temperomandibular joint disorders (Epstein and Marcoe, 1994; Hersh et al, 1994), cluster headache (following intranasal application) (Marks et al, 1993), osteoarthritis (McCarthy and McCarthy, 1992), and dermatological and cutaneous conditions (Hautkappe et al, 1998). Whereas pain relief is widely observed in these studies, the degree of relief is usually modest, although some patients have a very good result. Topical capsaicin is generally not considered a satisfactory sole therapy for chronic pain conditions and is often considered an adjuvant to other approaches (Watson, 1994). No significant benefit was reported in chronic distal painful neuropathy (Low et al, 1995) or with human immunodeficiency

virus-neuropathy (Paice et al, 2000).

SUMM The most frequently encountered adverse effect with capsaicin is burning pain at the site of application, particularly in the first week of application. This can make it impossible to blind trials. . . concentration (5-10%) under regional anesthesia, and this produced sustained analgesia lasting 1 to 8 weeks in cases of complex regional pain syndrome and neuropathic pain (Robbins et al, 1998). When topical local anesthetics were applied with 1% topical capsaicin, no alteration in pain produced by the capsaicin was observed in healthy subjects (Fuchs et al, 1999) indicating that this cotreatment was not sufficient to block the pain induced by capsaicin.

SUMM . . . its use. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain. . .

SUMM . . . of tramadol. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain. . .

SUMM . . . a concentration from greater than about 5% to about 10% by weight to be an extremely effective therapy for treating neuropathic pain, so long as an anesthetic, preferably by means of a transdermal patch, is administered initially to the affected area to. . .

SUMM . . . the analgesic drug is enhanced by the at least one nontoxic N-methyl-D-aspartate receptor antagonist. Preferably, the analgesic drug is an opioid analgesic, the at least one nontoxic N-methyl-D-aspartate receptor antagonist is dextromethorphan, and the analgesic composition is substantially free of opioid antagonist.

SUMM . . . the present invention, a NMDA receptor antagonist can be dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

DETD The pharmacological management of acute postoperative pain and chronic pain syndromes has been traditionally based on various regimens of opiates and their congeners or NSAIDs. All opiates have side effects,. . . may also induce side effects such as exacerbation of bleeding tendencies and the impairment renal function. The search for alternative pain control strategies has focused on the N-methyl-D-aspartate (NMDA) receptors and their antagonists which were recently shown to alleviate somatic and neuropathic pain sensation in both animal and human models (Plesan et al, 1998, Klepstad et al, 1990, Eisenberg et al, 1998, Kinnman. . . affinity binding of the drugs to NMDA receptors resulting in blockade of the NMDA receptors located at the junction where pain is generated by peripheral nociceptive stimuli and is thence conveyed to central receptors via A* and C sensory fibres (Woolf et al, 1993). From a clinical standpoint, the amounts of conventional pain killers that are needed for effective pain. control would be much smaller. One of these compounds is dextromethorphan (DM), a low affinity, non-competitive NMDA receptor antagonist that. . .

DETD . . . Rains and Bryson, 1995). Topical capsaicin produces benefit in postherpetic neuralgia (Bernstein et al, 1989; Watson et al, 1993),

diabetic neuropathy (Capsaicin Study Group, 1992), postmastectomy pain syndrome (Watson and Evans, 1992; Dini et al, 1993), oral neuropathic pain, trigeminal neuralgia, and temperomandibular joint disorders (Epstein and Marcoe, 1994; Hersh et al, 1994), cluster headache (following intranasal application) (Marks et al, 1993), osteoarthritis (McCarthy and McCarthy, 1992), and dermatological and cutaneous conditions (Hautkappe et al, 1998). Whereas pain relief is widely observed in these studies, the degree of relief is usually modest, although some patients have a very good result. Topical capsaicin is generally not considered a satisfactory sole therapy for chronic pain conditions and is often considered an adjuvant to other approaches (Watson, 1994). No significant benefit was reported in chronic distal painful neuropathy (Low et al, 1995) or with human immunodeficiency virus-neuropathy (Paice et al, 2000).

DETD The most frequently encountered adverse effect with capsaicin is burning pain at the site of application, particularly in the first week of application. This can make it impossible to blind trials. . . concentration (5-10%) under regional anesthesia, and this produced sustained analgesia lasting 1 to 8 weeks in cases of complex regional pain syndrome and neuropathic pain (Robbins et al, 1998). When topical local anesthetics were applied with 1% topical capsaicin, no alteration in pain produced by the capsaicin was observed in healthy subjects (Fuchs et al, 1999) indicating that this cotreatment was not sufficient to block the pain induced by capsaicin.

DETD . . . which may be utilized in the present invention include dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives, salts, metabolites or complexes thereof.

DETD . . . capsaicin or an ester of capsaicin and μ-opiate analgesic combination of the present invention. These diseases include moderate to severe pain arising from many different etiologies, including but not limited to cancer pain and post-surgical pain , fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases such as osteoarthritis, gout and ankylosing spondylitis, bursitis, burns, symptoms associated with diabetic neuropathy and injuries. Further, the combination of NMDA antagonist, capsaicin or an ester of capsaicin and μ-opiate analgesic is useful as. . .

DETD A 53 year old hispanic male has developed Type 2 diabetes a year ago and has diabetic neuropathy in the feet. He was given the capsules of composition 1 in example 4 and a 0.5% butyryl-capsaicin USP27 gel. . . the oil for the treatment of cold sores. "I was diagnosed with type 2 diabetes last year. I also have neuropathy in my feet. I had an ulcer on my foot and was treated by a local pediatric doctor in San. . . low-carb diet only, with no medication. I have also lost 40 lbs. since my diagnosis last year. I however feel pain on the bottom of my feet at times. Since taking the cream by application on my feet, I have noticed. . . to 24 hrs per-application. In addition, I started taking 1 capsules every 12 to 24 hours to further reduce my pain. I noticed that within a day, the pain is almost gone and I can sleep well during the night.

This cream and the capsules really help my condition. . .

DETD A 40 year old female developed diabetic neuropathy in 2000 and was given capsules of composition 1 in example 4 and 0.5% butyryl capsaicin cream for treating her pain in the feet. She gave the following testimony about the treatment. "I was diagnosed with neuropathy in 2000. There never has been much they could do for me other than give me pain medication that's addictive. At this time, I'm on Neurontin 1800 mg a day, Vicodin 5-6 tablets a day. Diclofenac 150. . . creme and within 30 min. I could feel the difference. Later I was up walking and realized there was no pain at all. I started taking the capsule 1-2 a day in addition to the topical cream. At night I don't sleep well because of the pain, but I was able to go to sleep the whole night through without cramps and pain. My cast was removed in few days and now I am applying the 0.5% cream on both of my feet. . . day and take 1-2 capsules a day. I have experienced excellent results and I am almost completely free of any pain now. I am no longer taking my prescribed pain medication for the past two weeks".

DETD A 49 year old male developed diabetic neuropathy in 2001 and was given 0.5% butyryl capsaicin USP27 gel and the capsules of composition 1 in example 4for treating his pain in the feet. He gave the following testimony about the treatment. "I have diabetic neuropathy brought on by extreme intra-venous application of antibiotics for a six day period. Since that time I have experienced unmanageable pain causing sleep depravation, anxiety with no relief on the market. Prescriptions for anti-depressants were given by my personal physician but. . . were marginally effective at best. Now I am also taking one capsule a day along with the cream and the pain is almost gone".

DETD A 62 year old female developed neuropathy in 1975 and was given 0.5% butyryl capsaicin USP27 gel and capsules of composition I in example 4 for treating her pain in the feet. She gave the following testimony about the treatment. "My neuropathy numbness in feet and hands first started after back surgery in 1975 my L 4 and 5 were fused and some disks removed. The numbness and pain increased after surgery for a double mastectomy which was botched by a Doctor inexperienced at this surgery in 1988 causing sever pain in my abdominal muscles and up my chest. In 1992 I was in the hospital for depression a new Doctor prescribed Percocet medication for my pain. The Percocet helped but I had to take 8 a day 5/325 mgs with anti depression medication at the time. The pain was so overwhelming after 4 years that I decided one day to end it all and I was found by my husband on the floor. I had kept my pain a secret over the 4 years hoping it would just eventually go away and I had never told my family that I was suffering so much. I had overdosed with the Percocet in an attempt to end my pain for good. I recovered some and I tried to cut back on the Percocet and got down to I a day to prevent addiction. The increase in pain and numbness was causing me to stumble when I walked. A neurologist in 1998 suggested that I try Neurontin which. . . starting to help some but they had to increase to 800 mgs 5 times a day to really help my pain. This helped more than the Percocet alone but I still needed to keep the Percocet at reduced amounts. I fell. . . again but in 2003 doctors had to use rods and pins to secure it. With each surgery my numbness and pain would increase. I tried water therapy and various physical therapies but nothing could relieve my pain. I have had other injuries as well, in 2002 a broken right ankle and compression fracture

in my right knee. . . switched me to a generic version of the same medication and dropped the dose to 50 mgs a day. My pain increased immediately and I went through withdrawals with the smaller dose. This Doctor said if the pain didn't decrease I was to increase one tablet more a day each week till the end of the 4.sup.th week. . . went back to this Doctor and just increased back to 800 mgs 5 times a day to coupe with the pain, burning, and itching feelings. I had to take depression medication again at this time. I tried a new topical cream. . . is weakening my bones. After seeing the remarkable result, now I am also taking 1-2 capsules a day and my pain is totally eliminated".

CLM What is claimed is:

. . . composition of claim 1, wherein the NMDA antagonist is dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

CLM What is claimed is:

. . . composition of claim 2, wherein the NMDA antagonist is dextromethorphan, dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, phencyclidine, MK-801, dizocilpine, CCPene, flupirtine, or derivatives or salts thereof.

IT 77-10-1, Phencyclidine 125-71-3, Dextromethorphan 125-73-5, Dextrorphan 137-66-6, Ascorbyl palmitate 768-94-5, Amantadine 2444-46-4, Nonivamide 2444-46-4D, Nonivamide, derivs. 6740-88-1, Ketamine 18609-21-7, Dextromethorphan hydrochloride 19408-84-5, Dihydrocapsaicin 19408-84-5D, Dihydrocapsaicin, derivs. 19982-08-2, Memantine 20279-06-5, Homodihydrocapsaicin 20279-06-5D, Homodihydrocapsaicin, derivs. 23210-56-2, Ifenprodil 25775-90-0, Civamide 25775-90-0D, Civamide, derivs. 27203-92-5, Tramadol 28789-35-7, Nordihydrocapsaicin 28789-35-7D, Nordihydrocapsaicin, derivs. 31078-36-1, n-Vanillyldecanamide 31078-36-1D, n-Vanillyldecanamide, derivs. 36282-47-0, Tramadol hydrochloride 56995-20-1, Flupirtine 58493-47-3, n-Vanillyloctanamide 58493-47-3D, n-Vanillyloctanamide, derivs. 58493-48-4, Homocapsaicin 58493-48-4D, Homocapsaicin, derivs. 77086-21-6, Dizocilpine 77086-22-7, MK 801 80456-81-1, O-Desmethyl tramadol 119431-25-3, Eliprodil 132014-88-1, Cppene 147441-56-3, Tramadol N-oxide
(novel pharmaceutical compns. for treating chronic pain and pain associated with neuropathy containing N-methyl-D-aspartate receptor antagonist
in combination with μ-opiate analgesic)

L9 ANSWER 4 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2008:44840 USPATFULL			
TITLE:	Methods and Compositions			
INVENTOR(S):	Nadeson, Raymond, Lethbridge, AUSTRALIA Tucker, Adam Paul, Hawthorn, AUSTRALIA Goodchild, Colin, Malvern, AUSTRALIA			
PATENT ASSIGNEE(S):	CNSBio Pty Ltd, Melbourne, AUSTRALIA (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20080039463	A1	20080214	
APPLICATION INFO.:	US 2004-574438	A1	20041216	(10)

WO 2004-AU1772 20041216
20070625 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	AU 2003-2003906981	20031216

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 5400, SEATTLE, WA, 98104, US
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1-42
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 2617
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions of flupirtine for management of neuropathic or inflammatory pain optionally including one or more other analgesics including opiates, NSAIDS and other active agents in immediate and controlled release forms.. . .

DRWD . . . carrageenan-induced hyperalgesia in male Wistar rats, where paw flick latency (seconds) is plotted against time (minutes) for saline controls (diamonds), flupirtine at 5 mg/kg (squares), flupirtine at 10 mg/kg (stars), morphine at 0.8 mg/kg (vertical bars), morphine at 1.6 mg/kg (horizontal bars), the combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg (squares) and the combination of flupirtine at 10 mg/kg with morphine at 0.4 mg/kg (circles).

DRWD . . . Wistar rats, where standardized ECT value as a ratio against the control is plotted against time for saline controls (triangles), flupirtine at 5 mg/kg (diamonds), morphine at 0.4 mg/kg (circles) and the combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg (squares); and

DRWD . . . threshold (grams) is plotted against time (minutes), where zero time is time of test drug injection, for saline controls (diamonds), flupirtine at 5 mg/kg (squares), flupirtine at 10 mg/kg (triangles), morphine at 1.6 mg/kg (crosses), morphine at 3.2 mg/kg (stars), the combination of flupirtine at 5 mg/kg with morphine at 3.2 mg/kg (closed circles) and the combination of flupirtine at 10 mg/kg with morphine at 1.6 mg/kg (open squares), with results for weight matched non-diabetic controls shown with an. . .

DETD The present invention relates generally to the field of pain management, and in particular, the management of neuropathic or inflammatory pain including a neuropathic or inflammatory component of nociceptive pain. More particularly, the present invention provides methods and compositions which treat, alleviate, prevent, diminish or otherwise ameliorate the symptoms of neuropathic or inflammatory pain. The present invention further contemplates combination therapy involved in the treatment of pain in association with the treatment of a particular disease condition or pathology. The present invention further also provides sustained and. . . stents, catheters and other mechanical devices coated with formulations which permit sustained or slow release of active ingredients involved in pain management.

DETD Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such

terms. In considering approaches to treatment of pain, it is important to understand the distinction between acute and persistent or chronic pain. Acute pain occurs as a result of tissue injury, and is mediated by chemical, mechanical or thermal stimulation of pain receptors known as nociceptors. In contrast to acute pain, chronic or persistent pain in itself constitutes a disease which serves no protective biological function. Chronic pain is unrelenting and can persist for years and frequently cannot be associated with a single injury. Chronic pain predominantly constitutes chronic inflammatory pain (e.g. arthritis) or "neuropathic pain" which can be defined as pain initiated or caused by a primary lesion or dysfunction within the nervous system (Mersky and Bogduk Classifications of Chronic Pain, 2.sup.nd edn. Seattle LASP Press: 394, 1994, De Andres and Garcia-Ribas Pain Practice 3:1-7, 2003). Neuropathic pain is associated with a variety of disease states and present in the clinic with a wide range of symptoms. (Woolf and Mannion Lancet 353:1959-64, 1999) It does not require specific pain receptor stimulation although such stimulation can add to the intensity of the pain sensation (Baron Clin J Pan 16 (suppl2):S12-S20, 2003).

DETD Neuropathic pain is often reported as having a lancinating or continuous burning character and is frequently associated with the appearance of abnormal sensory signs such as allodynia and hyperalgesia. Alloydnia is defined as pain resulting from a stimulus that does not normally elicit a painful response, and hyperalgesia is characterized by an increased pain response to normally non-painful stimuli. Some disorders characterized by neuropathic pain include monoradiculopathies, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain , complex regional pain syndromes, back pain and the various peripheral neuropathies. Neuropathic pain may also be associated with diabetes, radio- or chemo-therapy and infections such as HIV. Neuropathic pain may also result as a side effect of drug treatment or abuse.

DETD Neuropathic pain can be characterized by the following clinical features (Teng and Mekhail Pain Practice 3:8-12, 2003, Rajbhandari et al Pain, 83:627-629, 1999, Melzack et al Ann NY Acad Sci, 933:157-174, 2001):

1. There is the presence of an abnormal,. . . has a burning or electrical quality with an occasional paroxysmal, brief, shooting, or stabbing quality.
2. Although the onset of most neuropathic pain is within days after the precipitating injury, there is no absolute temporal relationship to the originating neural trauma such that it can begin weeks, months, or even years later.
3. Pain may be felt in a region of sensory deficit.
4. Non-noxious stimuli may be painful (allodynia).
5. Noxious stimuli may produce greater than normal response (hyperalgesia).
6. There may be an increase in the intensity of pain with repeated stimuli and the pain may persist after the removal of stimuli.

DETD There are no analgesic agents specific for one type of pain component over another and neuropathic and nociceptive pains often respond differently to various analgesics.

DETD Accordingly, although there are numerous available therapies for acute

pain caused by stimulation of the nociceptors, especially treatment with opioid and non-steroidal anti-inflammatory drugs (NSAIDs), neuropathic pain is an area of largely unmet therapeutic need. Due to the distinct pathophysiochemical mechanisms and clinical manifestations associated with neuropathic pain relative to pain caused as a result of nociceptor stimulation or acute pain, agents useful in the treatment of pain caused as a result of nociceptor stimulation or acute pain have reduced effectiveness in neuropathic pain treatment. In particular, the effectiveness of opioids in the treatment of neuropathic pain is diminished relative to their use in the treatment of pain caused as a result of nociceptor stimulation or acute pain, and drug dose response curves for treatment of neuropathic pain are shifted to the right of those for treatment of pain caused as a result of nociceptor stimulation or acute pain (Teng and Mekhail, 2003 supra, De Andres and Garcia-Ribas, 2003 supra, Stute et al J. Pain Symptom Management 25:1123-1131, 2003).

DETD Due to the diminished effects of opioids in subjects suffering from neuropathic pain, the use of opioids is often frequent and sustained. This over use is often associated with addiction, the development of tolerance and an increase in the number and severity of side effects associated with opioid use. These side effects include euphoric effects, emetic effects, spastic constipation and increased smooth muscle tone.

DETD The conventional pharmacological mainstays of clinical management of neuropathic pain are the tricyclic anti-depressants and certain anti-convulsants, but even these achieve a reduction in pain of less that 50% in greater than 50% of patients treated. These agents are also associated with significant side effect. . .

DETD There is a pressing need for improved regimes for the treatment of neuropathic and inflammatory pain as well as improved regimes for treating disease conditions which have a neuropathic or inflammatory pain component.

DETD The present invention provides methods and compositions which treat, alleviate, prevent, diminish or otherwise ameliorate the symptoms associated with neuropathic and/or inflammatory pain in a subject. Reference to "neuropathic pain" or "inflammatory pain" includes the neuropathic or inflammatory component of nociceptive pain. In particular, the present invention contemplates a method for inducing an analgesic response to neuropathic or inflammatory pain in a mammal comprising administering to the mammal an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the sensation of pain. In a related aspect, the compositions and methods of the present invention do not induce overt sedation and/or cause reduced side effects associated with agents used in the treatment of pain.

DETD The present invention also provides a method of inducing an analgesic response in a mammal suffering neuropathic or inflammatory pain by administering to the mammal one of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof concurrently, separately or sequentially with respect to the other of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof,

in an amount effective to reduce the level of or otherwise ameliorate the sensation of pain. Preferably, the flupirtine or a pharmaceutically acceptable salt derivate, homolog or analog thereof is administered in an amount effective to reduce at least. . . the method does not induce overt sedation such as caused by the analgesic agent. Preferably, the analgesic agent is an opioid, such as but not limited to fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene,. . . dihydromorphine, noscapine, papverine, papveretum, alfentanil, buprenorphine and tramadol and pharmaceutically acceptable salts, derivatives, homologs or analogs thereof as well as opioid agonists.

DETD Another embodiment the present invention relates to the use of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof in the manufacture of a medicament for inducing an analgesic response in the treatment of neuropathic or inflammatory pain. Preferably, the analgesia is induced without overt sedation and preferably the pain is neuropathic pain.

DETD In a further embodiment, the present invention relates to the use of an analgesic agent and flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, in the manufacture of one or more separate or combined medicaments for inducing analgesia in response to inflammatory or neuropathic pain. Preferably, the analgesia is induced without overt sedation and preferably the pain is neuropathic pain. In a preferred embodiment the analgesic agent is an opioid and preferably the opioid is selected from one or more of the opioids listed above or a pharmaceutically acceptable salt, derivatives, homologs or analogs. . .

DETD . . . or other pathology wherein the treatment of the disease, condition or pathology is conducted in association with pain management using flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof or optionally an opioid or another analgesic compound.

DETD . . . a still further embodiment of the present invention, there is provided a delivery system for inducing analgesia in response to neuropathic or inflammatory pain in a mammal comprising an analgesic agent and flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof. In a preferred embodiment the analgesic agent is an opioid and preferred the opioid is selected from one or more of the opioids listed above or pharmaceutically acceptable salts, derivatives, homologs or analogs thereof.. . .

DETD The present invention further provides a method of treatment of a condition such as cancer, back pain, inflammation or a neurological condition which has a neuropathic or inflammatory pain component, the treatment comprising the administration of flupirtine and optionally an opioid or a pharmaceutically acceptable salts, derivatives, homologs or analogs thereof.

DETD Preferably, the flupirtine or pharmaceutically acceptable salt, derivative, homolog or analog thereof is administered at a dose of between about 0.5 mg/kg and. . .

DETD A further aspect of the subject invention provides a system for the controlled release of flupirtine or a pharmaceutically

acceptable salt, derivative, homolog or analog thereof and optionally an opioid, alone or together with another analgesic or active agent, wherein the system comprises:

(a) a deposit-core comprising an effective. . .

DETD The present invention further provides an agent for inducing an analgesic response in a mammal, the agent comprising flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally an analgesic compound such as an opioid and optionally an active compound for treating a condition, disease or pathology. In one particular example, the present invention contemplates. . . a treatment protocol for cancer, the protocol comprising the administration of a anti-cancer agent and/or radiation therapy in combination with flupirtine and optionally an opioid or a pharmaceutically acceptable salt, derivative, homolog or analog thereof.

DETD . . . forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "an opioid" includes a single opioid, as well as two or more opioids; reference to "an analgesic agent" includes a single agent, as well as two. . .

DETD . . . "effective amount" and "therapeutically effective amount" of an agent as used herein mean a sufficient amount of the agent (e.g. flupirtine and/or an opioid) to provide the desired therapeutic or physiological effect or outcome. Undesirable effects, e.g. side effects, are sometimes manifested along with. . .

DETD The present invention provides a method of an inducing analgesic response to neuropathic or inflammatory pain in a mammal. In this context the term "mammal" is intended to encompass both humans and other mammals such as. . .

DETD Throughout this specification, the term "neuropathic pain" is to be understood to mean pain initiated or caused by a primary lesion or dysfunction within the nervous system. Examples of categories of neuropathic pain that may be treated by the methods of the present invention include monoradiculopathies, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, complex regional pain syndromes, back pain, neuropathic pain associated with AIDS and infection with the human immunodeficiency virus and the various peripheral neuropathies, including, but not limited to drug-induced and diabetic neuropathies.

DETD Reference to "neuropathic pain" or inflammatory pain" includes reference to a neuropathic or inflammatory component of nociceptive pain.

DETD The method according to the present invention to induces an analgesic response to neuropathic and/or inflammatory pain being suffered by a mammalian, preferably human, patient. A patient, in this context, is also referred to as a "subject",. . . "recipient". In this context the terms "analgesia" and "analgesic response" are intended to describe a state of reduced sensibility to pain, which preferably occurs without overt sedation and preferably without an effect upon the sense of touch. Preferably, the sensibility to pain is reduced by at least 30%, preferably at least 50%, more preferably at least 70% and particularly preferably at least 85%. In a most preferred aspect of the present invention, the sensibility to the neuropathic pain is completely, or substantially completely, removed. To assess the level of reduction of sensibility to

pain associated with the analgesia induced by the methods according to the present invention it is possible to conduct tests such as the short form McGill pain questionnaire and/or visual analogue scales for pain intensity and/or verbal rating scales for pain intensity and/or measurement of tactile allodynia using von Frey hairs or similar device. These tests are standard tests within the. . .

DETD Accordingly, one aspect of the present invention contemplates a method for inducing an analgesic response to neuropathic or inflammatory pain in a mammal comprising administering to the subject an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the sensation of pain.

DETD Another aspect of the present invention provides a method of inducing analgesia in a mammal suffering neuropathic or inflammatory pain by administering to the mammal one of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof concurrently, separately or sequentially with respect to the other of an analgesic agent or flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, in an amount effective to reduce the level of or otherwise ameliorate the sensation of pain.

DETD . . . or other pathology wherein the treatment of the disease, condition or pathology is conducted in association with pain management using flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally in addition to an analgesic agent.

DETD In both cases, the analgesic effect is preferably without overt sedation or the other side effects of flupirtine or the analgesic agent.

DETD Collectively, the flupirtine or pharmaceutically acceptable salt, derivative, homolog or analog thereof and the other analgesic agent will be referred to as the "active agents". A synergistically effective amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, when administered concurrently, separately or sequentially with an analgesic agent such as an opioid may restore or improve opioid responsiveness to neuropathic or inflammatory pain.

The active agents may be administered either as a combined form, i.e. a single composition containing the active agents, or. . .

DETD GABAergic drugs can also be used in combination with flupirtine for the treatment of neuropathic and inflammatory pain . GABAergic drugs include compounds that enhance the action of gamma aminobutyric acid (GABA) in the central nervous system; these include. . .

DETD As used herein, opioid compounds (opioids) include any compound that is physiologically acceptable in mammalian systems and is a full or at least partial agonist of an opioid receptor.

Opioid compounds are well known and include naturally occurring compounds derived from opium such as codeine, morphine and papavarine as well. . . as derivatives of such compounds that generally have structural similarity as well as other structurally unrelated compounds that agonise an opioid receptor present in a mammalian system.

Specific examples of opioid compounds contemplated by the present invention include: fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine,

diamorphine, pethidine, methadone,. . .

DETD . . . that the preferred route will vary with the condition and age of the subject, the nature of the inflammatory or neuropathic pain being treated, its location within the subject and the judgement of the physician or veterinarian. It will also be understood. . .

DETD . . . days, weeks or months. Suitable dosage amounts and regimes can be determined by the attending physician or veterinarian. For example, flupirtine or pharmaceutically acceptable salts, derivatives, homologs or analogs thereof, may be administered to a subject at a rate of between. . . 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours. Dosing of the analgesic agent, such as an opioid, can be determined by the attending physician in accordance with dosing rates in practice. For example, fentanyl can be administered. . .

DETD In relation to combination to therapy, flupirtine or its pharmaceutically acceptable salts, derivatives, homolog or analogs thereof and optionally together with an analgesic agent such as an opioid is used to manage pain and induce an analgesic response prior to, during or following treatment of a disease, condition. . .

DETD In one particular embodiment, flupirtine or its pharmaceutically acceptable salts, derivatives, homologs or analogs thereof and optionally an analgesic agent such as a opioid is used prior to, during or following cancer treatment. Examples of cancers which may be treated using this approach include. . . Uroplakins, Uterine sarcoma, Uterus Cancer, Vaginal Cancer, Vulva Cancer, Waldenstrom's-Macroglobulinemia or Wilms' Tumor. In some cases, the treatment potential of flupirtine and optionally an opioid and/or anti-cancer agent may also include a pronopshine.

DETD . . . protocol comprising the steps of administering to said subject, an effective amount of an anti-cancer agent and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the anticancer agent may be sequential or simultaneous or independent of the flupirtine.

DETD . . . protocol comprising the steps of administering to said subject, an effective amount of an anti-inflammatory agent and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the anti-inflammatory agent may be sequential or simultaneous or independent of the flupirtine.

DETD . . . of administering to said subject, an effective-amount of an agent used to treat a neurological condition and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . above. Administration of an agent used to treat a neurological disease may be sequential or simultaneous or independent of the flupirtine.

DETD In a further embodiment, combination therapy is in relation to reducing pain during the treatment of or amelioration of symptoms of any one or more of the following diseases which cause neuropathic pain or which have a neuropathic pain component: Abdominal Wall Defect, Abdominal Migraine, Achondrogenesis, Achondrogenesis Type IV, Achondrogenesis Type III, Achondroplasia, Achondroplasia Tarda, Achondroplastic Dwarfism, Acquired hnmunodeficiency. . . Barrett Ulcer, Benign Tumors of the Central

Nervous System, Bone Tumor-Epidermoid Cyst-Polyposis, Brachial Neuritis, Brachial Neuritis Syndrome, Brachial Plexus Neuritis, Brachial-Plexus-Neuropathy, Brachiocephalic Ischemia, Brain Tumors, Brain Tumors Benign, Brain Tumors Malignant, Brittle Bone Disease, Bullosa Hereditaria, Bullous CIE, Bullous Congenital Ichthyosiform. . . Chondroosteodystrophy, Chronic Adhesive Arachnoiditis, Chronic Idiopathic Polyneuritis (CIP), Chronic Inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Cicatricial Pemphigoid, Complex Regional Pain Syndrome, Congenital Cervical Synostosis, Congenital Dysmyelinating Neuropathy, Congenital Hypomyelinating Polyneuropathy, Congenital Hypomyelination Neuropathy, Congenital Hypomyelination, Congenital Hypomyelination (Onion Bulb) Polyneuropathy, Congenital Ichthyosiform Erythroderma, Congenital Tethered Cervical Spinal Cord Syndrome, Cranial Arteritis, Crohn's Disease,. . . Fibrous Ankylosis of Multiple Joints, Fibrous Dysplasia, Fragile X syndrome, Generalized Fibromatosis, Guillain-Barre Syndrome, Hemangiomatosis Chondrodystrophica, Hereditary Sensory and Autonomic Neuropathy Type I, Hereditary Sensory and Autonomic Neuropathy Type II, Hereditary Sensory and Autonomic Neuropathy Type III, Hereditary Sensory Motor Neuropathy , Hereditary Sensory Neuropathy type I, Hereditary Sensory Neuropathy Type I, Hereditary Sensory Neuropathy Type II, Hereditary Sensory Neuropathy Type m, Hereditary Sensory Radicular Neuropathy Type I, Hereditary Sensory Radicular Neuropathy Type I, Hereditary Sensory Radicular Neuropathy Type II, Herpes Zoster, Hodgkin Disease, Hodgkin's Disease, Hodgkin's Lymphoma, Hyperplastic Epidermolysis Bullosa, Hypertrophic Interstitial Neuropathy, Hypertrophic Interstitial Neuritis, Hypertrophic Interstitial Radiculoneuropathy, Hypertrophic Neuropathy of Refsum, Idiopathic Brachial Plexus Neuropathy, Idiopathic Cervical Dystonia, Juvenile (Childhood) Dermatomyositis (JDMS), Juvenile Diabetes, Juvenile Rheumatoid Arthritis, Pes Planus, Leg Ulcer, Lumbar Canal Stenosis, Lumbar. . . Cartilaginous Exostoses, Multiple Enchondromatosis, Multiple Myeloma, Multiple Neuritis of the Shoulder Girdle, Multiple Osteochondromatosis, Multiple Peripheral Neuritis, Multiple Sclerosis, Musculoskeletal Pain Syndrome, Neuropathic Amyloidosis, Neuropathic Beriberi, Neuropathy of Brachialpelxus Syndrome, Neuropathy Hereditary Sensory Type I, Neuropathy Hereditary Sensory Type II, Nieman Pick disease Type A (acute neuronopathic form), Nieman Pick disease Type B, Nieman Pick Disease Type C (chronic neuronopathic form), Non-Scarring Epidermolysis Bullosa, Ochronotic Arthritis, Ocular Herpes, Onion-Bulb Neuropathy, Osteogenesis Imperfect, Osteogenesis Imperfecta, Osteogenesis Imperfecta Congenita, Osteogenesis Imperfecta Tarda, Peripheral Neuritis, Peripheral Neuropathy, Perthes Disease, Polyarteritis Nodosa, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Polyneuritis Peripheral, Polyneuropathy Peripheral, Polyneuropathy and Polyradiculoneuropathy, Polyostotic Fibrous Dysplasia, Polyostotic Sclerosing Histiocytosis, Postmyelographic Arachnoiditis, Primary Progressive Multiple Sclerosis, Psoriasis, Radial Nerve Palsy, Radicular Neuropathy Sensory, Radicular Neuropathy Sensory Recessive, Reflex Sympathetic Dystrophy Syndrome, Relapsing-Remitting Multiple Sclerosis, Sensory Neuropathy Hereditary Type I, Sensory Neuropathy Hereditary Type II, Sensory Neuropathy Hereditary Type I,

Sensory Radicular Neuropathy, Sensory Radicular Neuropathy Recessive, Sickle Cell Anemia, Sickle Cell Disease, Sickle Cell-Hemoglobin C Disease, Sickle Cell-Hemoglobin D Disease, Sickle Cell-Thalassemia Disease, Sickle Cell. . . Arteritis, Temporal Arteritis, Tethered Spinal Cord Syndrome, Tethered Cord Malformation Sequence, Tethered Cord Syndrome, Tethered Cervical Spinal Cord Syndrome, Thalamic Pain Syndrome, Thalamic Hyperesthetic Anesthesia, Trigeminal Neuralgia, Variegate Porphyria, Vertebral Ankylosing Hyperostosis amongst others.

DETD . . . comprising the steps of administering to said subject, an effective amount of an a disease condition and an amount of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof effective to reduce the level of or otherwise ameliorate the. . . include any of those listed above. Administration of the disease condition may be sequential or simultaneous or independent of the flupirtine.

DETD The present invention also relates to compositions comprising flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof, optionally with another analgesic agent such as an opioid, together with one or more pharmaceutically acceptable additives and optionally other medicaments. The pharmaceutically acceptable additives may be in the. . .

DETD . . . present invention may be packaged for sale with other active agents or alternatively, other active agents may be formulated with flupirtine or its pharmaceutical salts, derivatives, homologs or analogs thereof and optionally an analgesic agent such as an opioid.

DETD Thus, a further particular aspect of the present invention provides a system for the controlled release of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof and optionally an opioid, alone or together with another analgesic or active agent, wherein the system comprises:

(a) a deposit-core comprising an effective. . .

DETD In another embodiment, a multiparticulate release flupirtine composition for oral administration is provided. The formulation is made by complexing flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof optionally together with an opioid and/or other analgesic or active agent with an ion-exchange resin in the form of small particles, typically less than 150. . .

DETD Still another aspect of the present invention provides a composition comprising: (a) a flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof; (b) an active component having a delayed time of release; and (c) an immediate release opioid removal component.

DETD The opioid may be alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, benzitramide, bupernorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dexocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol,. . .

DETD The opioid may be either an immediate release agonist or an agonist having a delayed time of release.

DETD . . . improver is water-soluble polyethoxylated caster oil and an example of a suitable surfactant is Cremophor EL. Dose ranges suitable for flupirtine or pharmaceutical salts, derivatives, homologs or analogs thereof are for example 100 to 1500 mg orally, every six

hours including. . .

DETD In combination with flupirtine, the dosage intervals are preferably from about 12 to 24 hours.

DETD . . . devices for introduction to or in a body or body cavity coated with a sustained or slow release formulation of flupirtine or a pharmaceutically acceptable salt, derivative, homolog or analog thereof. Optionally, an opioid alone or with other active agents is also included. Examples of mechanical devices include stents, catheters, artificial limbs, pins, needles. . .

DETD The present invention further provides an implantable medical device having an outer surface covered at least in part by a flupirtine or a pharmaceutically acceptable salts, derivative, homolog or analog and optionally an opioid and/or other active agent, a conformal coating of a hydrophobic elastomeric material incorporating an amount of active material therein for. . .

DETD . . . the ability to avoid side effects such as sedative effects of morphine or its homology, when used in combination with flupirtine.

DETD . . . The identified non-sedative doses of drugs used singly and in combination were then tested for antinociceptive effects in models of pain, where the following nociceptive paradigms were adopted:

(a) the electrical current threshold test (Example 2);
(b) carrageenan-induced paw inflammation (Example 3); and
(c) streptozotocin-induced diabetic neuropathy (Example 4).

DETD . . . as above with the following treatments:

(a) Saline
(b) Morphine at doses of 0.4, 0.8, 1.6, 3.2, and 6.4 mg/kg
(c) Flupirtine at doses of 5, 10 and 20 mg/kg
(d) A combination of flupirtine at 5 mg/kg with morphine at 0.4 mg/kg
(e) A combination of flupirtine at 10 mg/kg with morphine at 1.6 mg/kg

DETD

TABLE 1

Treatment	Lowest run time (s) n	mean	SD
saline control	30	119.2	2.8
flupirtine 5 mg/kg ip alone	18	118.4	6.1
flupirtine 10 mg/kg ip alone	20	107.7	36.7
flupirtine 20 mg/kg ip alone*	10	58.1*	54.5
morphine 0.4 mg/kg ip alone	10	120	0
morphine 0.8 mg/kg ip alone	10	120. . .	1.6 mg/kg ip alone 10 110.4 19
morphine 3.2 mg/kg ip alone	10	99.6	41.7
morphine 6.4 mg/kg ip alone*	10	60*	41.7
flupirtine 5.0 mg/kg + morphine 0.4 mg/kg together ip	10	119.5	1.3
flupirtine 10 mg/kg + morphine 1.6 mg/kg together ip	10	117	4.45

one way Anova + Tukey-Kramer post-hoc test: compared with saline control

*p. . .

DETD It can be concluded from these experiments that sedation is caused by doses of flupirtine greater than 10 mg/kg and morphine greater

than 3.2 mg/kg.
DETD The following drug treatments were given to separate groups of rats:

Saline controls
Flupirtine at doses of 5 and 10 mg/kg alone
Morphine at doses of 0.4, 0.8 and 1.6 mg/kg alone
Combinations of flupirtine at 5 and 10 mg/kg with morphine at 0.4 mg/kg
DETD
TABLE 2

Treatment	Pre-treatment mean	SD	n	Post-treatment mean	SD	n
saline controls	10.98	2.27	72	6.22	2.18	72
flupirtine 5 mg/kg ip alone	10.90	2.80	30	5.82	1.70	30
flupirtine 10 mg/kg alone	10.97	2.42	24	5.51	2.13	24
morphine 0.4 mg/kg ip alone	12.10	2.30	36	5.76	3.10	36
morphine 0.8 mg/kg alone	10.02	1.75	27	4.88	1.67	27
morphine 1.6 mg/kg alone	10.30	2.48	72	8.88	3.15	72
flupirtine 5 mg/kg and morphine 0.4 mg/kg ip together	11.60	2.25	72	8.75	3.31	72
flupirtine 10 mg/kg and morphine 0.4 mg/kg ip together	9.66	1.46	54	10.34	4.02	54

DETD Flupirtine 5 and 10 mg/kg or morphine 0.4 and 0.8 mg/kg alone had no effect on carrageenan-induced hyperalgesia. The combination of flupirtine 5 mg/kg with morphine 0.4 mg/kg caused significant reversal of carrageenan-induced hyperalgesia and this was equal to the effect of 1.6 mg/kg morphine given alone; flupirtine increased the antinociceptive effect of morphine fourfold. Flupirtine 5 mg/kg in combination with morphine 0.4 mg/kg led to significantly less hyperalgesia compared with saline or either drug alone. . . *p<0.001 one way ANOVA with Tukey-Kramer post hoc test. Finally, complete reversal of carrageenan-induced hyperalgesia was caused by 10 mg/kg flupirtine in combination with 0.4 mg/kg morphine i.e., doses of two drugs that were ineffective when given alone caused complete antinociception in this model of neuropathic pain (p>0.05 in comparison with pre carrageenan levels (at -20, -10 and 0 mins in graph above)--one way ANOVA with Tukey-Kramer. . .
DETD . . . and plotted as time response curves shown in FIG. 2 for groups of rats that received the following treatments:

Flupirtine at a dose of 5 mg/kg ip alone
Flupirtine at a dose of 10 mg/kg ip alone
Morphine at a dose of 0.4 mg/kg ip alone
A combination of morphine at a dose of 0.4 mg/kg with flupirtine at a dose of 5 mg/kg
DETD . . . 3

SUMMARY DATA ECT PARADIGM		n rats	n observations	mean	SD
saline controls	per	16	48	1.00	0.05
	post		90	1.27	0.35
flupirtine 5 mg/kg	pre	20	60	1.00	0.05
	post		100	1.54	0.64

flupirtine 10 mg/kg	pre	4	12	1.00	0.07
	post		20	1.92	0.79
morphine 0.4 mg/kg	pre	12	36	1.00	0.06
	post		60	1.46	0.53
combination morphine	pre	12	36	1.00	0.09
0.4 mg/kg and flupirtine	post		60	1.91	0.89
5 mg/kg					

DETD . . . one way ANOVA with Tukey-Kramer post hoc test was applied to the data in the table above. ECT values after flupirtine 5 or 10 mg/kg, morphine 0.4 mg/kg or the combination of morphine 0.4 mg/kg with flupirtine 5 mg/kg were all significantly greater than saline ($p<0.001$). There was significant antinociception following flupirtine alone at 5 or 10 mg/kg and morphine 0.4 mg/kg ($p<0.001$). The amount of antinociception following morphine 0.4 mg/kg/ flupirtine 5 mg/kg combination was significantly greater than morphine 0.4 mg/kg or flupirtine 5 mg/kg given alone ($p<0.001$). It is therefore concluded that non-sedative doses of flupirtine can increase the antinociception following morphine without causing sedation.

DETD The treatment of neuropathic pain states, including diabetic neuropathy in humans is frequently unsatisfactory. Current pharmacological regimens consist of the tricyclic antidepressants (Sindrup et al., Pain, 42:135-144, 1990; Max, M. B., Pain, 42:131-133, 1990; Max, M. B., Pain, 50:3-4, 1992), anticonvulsants, systemic local anaesthetics (lignocaine) and mexiletine and, more recently, GABApentin. All have limited success (Arner et al., Pain, 33:11-23, 1988; Davis et al., Pharmacology, Biochemistry and Behavior, 39:737-742, 1991; Galer, B. S., Neurology, 45: Suppl. 9 S17-S25, 1995; Avidan et al., Israel Journal of Medical Sciences, 32:331-334, 1996). It is accepted generally that human neuropathic pain states are resistant to opioid treatment (Arner et al. supra). Some researchers have found that opioids may produce antinociceptive effects in neuropathic pain models but at higher than normal doses that also cause sedation revealed by tests such as open field activity monitoring. . . test. This indicates a shift of the dose-response curve to the right, beyond the normal therapeutic range. (Portenoy et al., Pain. 43(3):273-86, 1990)

DETD Courteix and co-workers have developed a diabetes-induced model for neuropathic pain. They found that induction of experimental insulin-dependent diabetes mellitus in rats caused allodynia and hyperalgesia (Courteix et al., Pain, 53:81-88, 1993). They went on to show that intravenous morphine induced a dose-dependent antinociceptive effect at doses twice as high as those in normal rats, using the mechanical nociceptive paw pressure test (Courteix et al., Pain, 53 supra). Thus the diabetic model reproduced the experience of diabetic neuropathic pain in humans; it is opioid resistant. The experiments reported here use this model to assess the relative efficacy of flupirtine and morphine given alone and in combinations in causing antinociception assessed with paw pressure measured using the Randall Sellito method.

DETD . . . pressure nociceptive thresholds below 30 g (60% of the value in normal weight matched rats) were deemed to have developed hyperalgesia/ neuropathic pain and thus used in further experiments.

DETD . . . also at 20, 30 and 40 minutes after intraperitoneal (ip) injections of:

saline (controls)
weight matched non diabetic controls (no treatment)
  flupirtine 5 mg/kg alone
  flupirtine 10 mg/kg alone
morphine 1.6 mg/kg alone
morphine 3.2 mg/kg alone
  flupirtine 5 mg/kg plus morphine 3.2 mg/kg together
  flupirtine 10 mg/kg plus morphine 1.6 mg/kg together
DETD . . . diabetic controls n = 21 rats 63 44.7 6.9
saline controls n = 16 rats 48 28.54 4.12
48 30.94 5.89
flupirtine 5 mg/kg alone n = 21 rats 63
28.25 4.50 63 31.90 7.15
flupirtine 10 mg/kg alone n = 15 rats 45
27.89 5.69 45 41.00 14.56
morphine 1.6 mg/kg alone n = 14 rats 42 28.10 5.84
42 31.90 6.98
morphine 3.2 mg/kg alone n = 8 rats 24 26.67 4.82
24 35.00 10.11
flupirtine 5 mg/kg + morphine 3.2 mg/kg together n = 8 24
26.67 4.08 24 36.88 12.84
rats
flupirtine 10 mg/kg + morphine 1.6 mg/kg together n = 17 51
28.82 5.16 51 49.41 15.55
rats
DETD Complete reversal of streptozotocin-induced diabetic hyperalgesia was caused by flupirtine 10 mg/kg given alone and also flupirtine 10 mg/kg+morphine 1.6 mg/kg together ($p>0.05$); i.e., the paw withdrawal thresholds after the drug treatment were not statistically different from thresholds for normal non-diabetic weight matched controls. Flupirtine 5 mg/kg alone and morphine 1.6 mg/kg alone cause no significant reversal of diabetes-induced hyperalgesia; the paw withdrawal thresholds after. . . a lower dose of morphine (1.6 mg/kg shown to be ineffective when it was given alone) given in combination with flupirtine 10 mg/kg ($p<0.001$). Finally, flupirtine 10 mg/kg in combination with morphine 1.6 mg/kg caused greater antinociception than flupirtine 10 mg/kg alone.

DETD The results reported in Examples 2 through 4 show that non-sedative doses of flupirtine increases the overall antinociceptive effect of morphine without causing sedation in three animal models of pain; electrical, inflammatory and neuropathic. In neuropathic and inflammatory pain models it is possible, using flupirtine in combination with morphine, to cause such significant antinociception as to reverse hyperalgesia such that animals with these pain states are rendered normal with respect to pain sensitivity. This demonstrates utility of flupirtine as an adjunct to opioid analgesics especially in pain states such as inflammatory and neuropathic pain, which are either opioid resistant to the extent that only partial analgesia can be achieved with opioid drugs or are at doses that cause side effects such as sedation. The co-administration of flupirtine with the opioid offers improved pain control in inflammatory and neuropathic pain with doses and combinations that are not accompanied by sedation.

DETD Clinical Applications of Flupirtine
DETD . . . establish outcomes and variables that might be most useful to evaluate in larger double blind studies
Show that the administration of flupirtine to cancer patients with neuropathic pain can improve pain experience
Define the dose
Quantify the pain reduction along with reduction in the use of other analgesics, including morphine
Estimate the impact on quality of life
Show an improvement. . .
DETD The trial design was an open label dose escalation study carried out on patients with pain associated with cancer that has neuropathic elements as described below. Ethics committee approval and written informed consent from each patient were obtained. All patients referred to the palliative care unit with cancer-related neuropathic pain were considered eligible for entry if they had been receiving opioids for at least 48 hours. The trial lasted eight days. On day 0 the patients were assessed with respect to pain and side effect experiences as well as drug usage. On day 1 there was 24 hours observation and baseline measurements before commencement on flupirtine at a dose of 100 mg four times daily (qid). If the pain was not controlled and there was no evidence of dose limiting side effects as judged by the patient or clinician,. . . the dose could be escalated by 100 mg qid to a maximum of 300 mg qid. Once the patient was pain-free, there was no further dose escalation. Dose increases were only be made if the patient agreed and at the physicians' discretion, taking into account the general clinical situation, pain response, and any toxicity noted. Background "sustained release" and immediate release opioid dosage and other "adjunctive" analgesic drugs were reviewed on a daily basis as is normal practice and they were adjusted in dosage up or down according to clinical need. Patients were encouraged to take their normal opioid and co-analgesics concurrently including any "breakthrough" doses of immediate release morphine mixture.
DETD . . . of the disease into his pelvis and developed liver and pelvic metastases in early 2003. JE had been experiencing intermittent neuropathic pain in his left thigh and buttock for the last two years prior to presentation for a trial of flupirtine . This had been increasing in the two weeks prior to his admission. He described his pain as "a blow torch moving up and down his leg". He also complained of numbness in his left upper thigh.. . . (Kapanol) 50 mg mane and 100 mg nocte with immediate release morphine mixture (Ordine) 80 mg as required for breakthrough pain. This regimen has been unsuccessful in managing his pain. JE was commenced on an anticonvulsant (sodium valproate-Epilim) and a tricyclic antidepressant (amitryptyline--Endep) 6 days prior to admission and dexamethasone. . .
DETD Summary of Events During Flupirtine Trial (See Accompanying Table)
DETD Day 0: JE was admitted into the in-patient palliative care facility. His opioid usage for the previous 24 hours was 150 mg Kapanol and 260 mg Ordine together with dexamethasone 4 mg daily plus Epilim 600 mg and Endep 25 mg. His neuropathic pain discriminant function score: was 0.862. This is a function calculated from measurements of twelve different symptoms widely accepted to be indicative of neuropathic pain; a score >0 indicates

that the pain is neuropathic (Krause and Backonja. The Clinical Journal of Pain 19: 306-314 2003). His average pain score: 7/10, least pain: 4/10 and worst pain: 10/10. WHO performance status was 2 [fully active=0 and the other end of the scale, 4=completely disabled]. At that time,. . . unsteady. He had lower limb proximal weakness and a global deficit in sensation to pin prick. He felt that the pain was having a significant impact on his life, as he was unable to-get around to enjoy time with family and. . .

DETD Day 1: In the 24 hours before commencement on flupirtine JE's opioid usage was 100 mg Kapanol and 310 mg Ordine plus adjuncts: dexamethasone 4 mg; Epilim 600 mg; Endep 25 mg. Neuropathic pain discriminant score: was 2.448, average pain score: 8/10, least pain: 1/10 and worst pain: 10/10. WHO performance status was scored as 3. JE was still experiencing a considerable amount of drowsiness (4), poor appetite. . .

DETD Day 2: JE had been taking flupirtine 100 mg QID for 24 hours. Opioid usage for last 24 hours was 150 mg Kapanol with adjuncts: dexamethasone 4 mg; Epilim 600 mg; Endep 25 mg and paracetamol 1 g. His discriminant neuropathic pain score had fallen to a non-neuropathic level: -1.238. The average pain score was 2/10, least pain: 0/10, worst pain: 3/10 and WHO performance status: 3. At this stage JE was still quite drowsy (4) and his colostomy (3) had. . . to the palliative care unit. He also developed an occasional intention related myoclonic twitch in his right hand (2). JE's pain had almost completely disappeared and he was enjoying a good appetite and increased ease of movement.

DETD Day 3: JE continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 150 mg Kapanol plus adjuncts: dexamethasone 4 mg daily, Epilim 600 mg daily and Endep 25 mg. His neuropathic pain discriminant score had fallen to the minimum level indicating no pain at all: -1.408. His average pain score: 0/10; least pain: 0/10; worst pain : 0/10; and WHO performance status had improved: 2. JE was still quite drowsy (3) and an occasional myoclonic twitch was still present (2). He reported that he was feeling "very well", his appetite had increased and he had no pain at all. The flupirtine dose for the next 24 hours was increased to 200 mg QID and Kapanol reduced by 30 mg/24 hours.

DETD Day 4: JE was taking flupirtine 200 mg QID. Opioid usage for last 24 hours: 120 mg Kapanol with adjuncts: dexamethasone 4 mg daily; Epilim 600 mg daily; Endep 25 mg. His neuropathic pain discriminant score remained at the minimum score of -1.408. Average pain score: 0/10; least pain: 0/10; worst pain: 0/10 and WHO performance status: 3. However there were increased side effects. JE was no longer able to self-care, due. . . colostomy was also yet to function (2). However, he had not experienced any fullness and his appetite remained good. The flupirtine dose was reduced to 100 mg QID and the Kapanol to 80 mg/24 hours.

DETD Day 5: JE continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 80 mg Kapanol and adjuncts: dexamethasone 4 mg daily; Epilim 600 mg daily and Endep 25 mg. The neuropathic pain discriminant score remained at the minimum score of -1.408. The average pain score: 0/10; least pain: 0/10; worst pain: 6/10 and WHO performance status deteriorated: 4. JE had an accidental fall in the early hours of the morning whilst. . .

DETD Day 6: The flupirtine dose remained at 100 mg QID. Opioid usage for last 24 hours: 40 mg Kapanol and adjuncts: dexamethasone 2 mg plus Endep 25 mg only. His neuropathic pain discriminant score: -1.048, average pain score: 8/10, least pain: 0/10, worst pain: 9/10 and WHO performance status: 3. JE was less sedated at the time of assessment (3), and he was able. . .

DETD Day 7: JE continued to take flupirtine at the dose of 100 mg QID. Opioid usage for last 24 hours: 40 mg Kapanol with adjuncts: dexamethasone 2 mg and Endep 25 mg. His neuropathic pain discriminant score had returned to the minimum score of -1.408. His average pain score: 0/10; least pain: 0/10; worst pain: 4/10; and WHO performance status: 3. JE was still experiencing some drowsiness (3) and the myoclonic twitch (2). However, he was able to concentrate for longer periods and remained free from neuropathic pain symptoms. His appetite remained poor (3). However, his colostomy was functioning regularly. JE had also complained of spider hallucinations (2),. . .

DETD Day 8: JE continued to take flupirtine 100 mg QID. Opioid usage for the previous 24 hours: 40 mg Oxycontin (sustained release oxycodone)+5 mg Endone (immediate release oxycodone). Oxycodone is approximately twice as potent as morphine and thus JE was taking opioid at a dose equivalent to 90 mg morphine. He also took dexamethasone 2 mg. The neuropathic pain discriminant score was 0.677 with average pain score for the previous 24 hours: 7/10; least pain: 0/10; worst pain : 9/10 and WHO performance status: 3. JE had a numb left foot overnight that kept him awake. He was otherwise. . .

DETD Summary of Events after Flupirtine Trial

DETD On the following day JE was discharged home taking flupirtine dose 100 mg QID with Oxycontin 40 mg/24 hrs. His average pain score for the previous 24 hours was 0/10,. . .

DETD Day 18: JE at home, taking flupirtine dose 100 mg QID, Oxycontin 20 mg BD. endone 5 mg for breakthrough required 2-3 during the week and dexamethasone 4 mg for a low platelet count. He had no neuropathic pain symptoms. He said that he was "feeling well, eating everything and getting out and about. JE was still active at the last follow up on day 44 with no neuropathic pain symptoms taking Oxycontin 20 mg bd with no breakthroughs and leading an active life.

DETD . . . DAY OF OBSERVATION

OBSERVATIONS	DAY 0	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8
flupirtine dose in last 24 hours	0 mg	0 mg	100 mg	100 mg	100 mg	200 mg	100 mg	100 mg	100. . . 0 mg	0 mg	0 mg	0 mg	0 mg
metoclopramide, antiemetic									
WHO PERFORMANCE STATUS	2	3	3	2	3	4	3	3	3
neuropathic dwascriminant function score calculated from:	0.862	2.448	-1.238	-1.408	-1.408	-1.408	-1.408	-1.048	-1.408	0.677*
burning pain score	100	90	20	0	0	0	0	0	0
score for overly sensitive to	0	95	0	0					

0 0 0 0 0
touch
for shooting pain score 90 95 10 0
0 0 0 0 0
numbness score 60 95 0 0
0 0 0 0 90
electric pain score 0 95 0 0
0 0 0 0 0
tingling pain score 0 95 0 0
0 0 0 0 0
squeezing pain score 70 0 0 0
0 0 0 0 0
freezing pain score 0 0 0 0
0 0 0 0 0
unpleasant pain score 100 95 0 0
0 0 0 0 95
overwhelming pain score 100 98 0 0
0 0 40 0 95
score for increased pain due to 0 0 0 0
0 0 80 0 0
touch
score for increased pain due 0 0 0 0
0 0 0 0 0
to weather changes
AVERAGE PAIN LAST 7 8 2 0
0 0 8 0 7
24 HOURS
LEAST PAIN LAST 24 HRS 4 1 0 0
0 0 0 0 0*
PAIN SCORE RIGHT NOW 4 1 0 0
0 0 8 0 9
WORST PAIN SCORE LAST 10 10 2 0
0 6 9 4 9*
24 HOURS
PERCENTAGE PAIN RELIEF N/A N/A N/A
N/A N/A N/A N/A N/A N/A
LAST 24 HOURS
SCORE GENERAL ACTIVITY 8 5 1 1
1 1. . .

DETD . . . of metastases in RM's sacrum or hip. He was admitted to hospital in because of decreased mobility caused by ongoing pain in his left buttock and leg. He also had a right side foot drop and absent right ankle jerk but. . . showed a solitary metastasis of S2 with no cauda equina or nerve root involvement. RM had been experiencing fairly constant neuropathic type pain in his right buttock and leg since for four months prior to the study. The pain was initially experienced in his left leg and hip and then as time went on, it spread towards and down his right side. On admission for the study, the pain was concentrated down his right side. RM described a "burning" pain that radiated from his hip and down his leg. The pain was always present but it tended to be worst in the mornings. RM had experienced little improvement with analgesics. He. . . release oxycodone 20 mg BD with immediate release Endone 5 mg and hydromorphone 1 mg sc. as required for breakthrough pain. RM was treated with ketaminefor six days prior to this trial; it was ceased 24 hours before flupirtine dosing began. The ketamine failed to control pain and neuropathic

pain scores increased towards the end of that treatment (see table below comparing day 0 with day 1. In an attempt to control the pain RM was also commenced on a cox-2 inhibitor (Celebrex) and an anticonvulsant (Gabapentin) in the weeks before the flupirtine trial began. This regimen had also been unsuccessful in managing his pain.

DETD Summary of Events During Flupirtine Trial

DETD Day 0: RM was admitted into the in-patient palliative care facility. His opioid usage for the previous 24 hours was 40 mg oxycodone orally and 1.5 mg hydromorphone subcutaneously together with Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. In spite of this treatment he still had significant neuropathic pain; his neuropathic pain discriminant function score: was 0.077. This is a function calculated from measurements of twelve different symptoms widely accepted to be indicative of neuropathic pain; a score >0 indicates that the pain is neuropathic (Development of a Neuropathic Pain Questionnaire. Krause and Backonja, The Clinical Journal of Pain 19: 306-314, 2003). His average pain score: 5/10, least pain: 0/10 and worst pain: 10/10. WHO performance status was 3 [fully active=0 and the other end of the scale, 4=completely disabled]. At that time. . . amount of constipation, poor appetite and unsteady gait (walks with the aid of a wheelie frame). He felt that the pain was having a significant impact on his life, as it seemed the pain was always present.

DETD Day 1: In the 24 hours before commencement on flupirtine RM's opioid usage was: 40 mg oxycodone orally, 15 mg Endone orally and 0.5 mg hydromorphone subcutaneously plus adjuncts: Gabapentin 100 mg. . . hourly Paracetamol. RM was receiving ketamine prior to his transfer, a period of 20.sup.+ hours elapsed before his commencement on flupirtine. Neuropathic pain discriminant score was highly significant at the value of 0.262. His average pain score: 8/10, least pain: 0/10 and worst pain: 10/10. WHO performance status was scored as 3. RM was experiencing poor appetite (4), unsteady gait (4), nausea (3) and. . .

DETD Day 2: RM had been taking flupirtine 100 mg QID for 24 hours. Opioid usage for last 24 hours: 40 mg oxycodone orally and 2.5 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score had fallen dramatically to a non-neuropathic level: -0.228. The average pain score had also fallen to 5/10, least pain: 0/10, worst pain: 8/10 and WHO performance status: 3. RM's appetite remained poor (3), as did his gait (4). He was also drowsy. . .

DETD Day 3: RM continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 2 mg hydromorphone subcutaneously plus adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained at a low non-neuropathic level: -1.008. His average pain score: 8/10; least pain: 0/10; worst pain: 8/10; and WHO performance status: 3. RM was less drowsy (2) and remained unsteady on his feet (4). RM reported. . .

DETD Day 4: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone and 5 mg Endone both orally, no hydromorphone breakthrough injections, with adjuncts:

Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remaine low and at a non-neuropathic level: -1.138. Average pain score: 8/10; least pain: 0/10; worst pain : 8/10 and WHO performance status: 3. RM feels that his pain relief had improved, it now feels "Like a bruise". RM had a short bout of nausea (2) in the morning. . . gait remained unsteady (4); nevertheless he was quite active walking around the unit to the lounge. RM thinks that the pain relief was much better today. He reported that 75% pain relief had been achieved. This compared markedly with the 10% relief he reported on day 1 before treatment with flupirtine.

DETD Day 5: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 1 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score: -1.003. The average pain score: 8/10; least pain: 2/10; worst pain: 9/10 and WHO performance status: 3. RM was experiencing some constipation (2), poor appetite (2), and unsteady gait (4). He. . . difficult to concentrate (2) on the questionnaire with his mind tending to wander. He still reported a high percentage of pain relief.

DETD Day 6: RM continued taking flupirtine 100 mg QID. Opioid usage for last 24 hours: 40 mg oxycodone orally and 3 mg hydromorphone subcutaneously with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained low and non-neuropathic : -1.168. This indicated that the pain being experienced was not of neuropathic origin. The average pain score had decreased: 4/10; least pain: 2/10; worst pain: 7/10 and WHO performance status: 3. The neuropathic element to RM's pain appeared to have improved from the first day of taking flupirtine. However he was still experiencing a significant amount of incident pain. Since the reason for addition of flupirtine was to treat the opioid resistant neuropathic pain, the dosage was kept the same but opioid dose was increased, to 30 mg oxycodone orally BD. This follows the concept of this invention of using a combination of opioid with flupirtine in the management of pain states that involve a significant neuropathic pain element that is resistant to the opioid given on its own. He still had some loss of appetite (2), constipation (2), poor concentration (2) and nausea (2).. . .

DETD Day 7: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 60 mg oxycodone and 10 mg Endone both orally with adjuncts: Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score remained low and non-neuropathic: -1.168. The other pain-scores had all fallen: average pain score 3/10; least pain 0/10; worst pain 5/10. WHO performance status remained at 3. RM seemed to be a little flat. He admitted to feeling "a bit down today". He felt that the pain had eased but that he still "wasn't right". RM complained that there was not much to do in the unit. . .

DETD Day 8: RM continued to take flupirtine 100 mg QID. Opioid usage for last 24 hours: 60 mg oxycodone, 5 mg Endone both orally and 2 mg hydromorphone subcutaneously with adjuncts:

Gabapentin 100 mg daily, Celebrex 400 mg and strict 6 hourly Paracetamol. Neuropathic pain discriminant score: -1.198. The average pain score: 4/10; least pain: 1/10; worst pain: 7/10 and WHO performance status: 3. RM had experienced two bouts of nausea (3) requiring 10 mg maxalon on both. . . (2) had been poor at times. He was constipated (3) and had received his regular aperients. RM felt that the flupirtine had "been good" even though his pain is still present and wished to remain on his current dose after discharge from the palliative care unit.

DETD . . . DAY OF OBSERVATION									
OBSERVATIONS					DAY 0	DAY 1	DAY 2	DAY 3	
DAY 4	DAY 5	DAY 6	DAY 7	DAY 8					
flupirtine dose in last 24 hours					0 mg	0 mg	100		
mg	100 mg	100 mg	100 mg	100 mg	100.	. .	mg	0 mg	
10 mg	0 mg	20 mg							
WHO PERFORMANCE STATUS					3	3	3	3	
3	3	3	3	3					
neuropathic discriminant function score					0.077	0.262			
-0.228	-1.008	-1.138	-1.003	-1.168	-1.168	-1.198*			
calculated from:									
burning pain score					100	90	70		
0	0	0	0	0	0*				
score for overly sensitive to touch					50	20	0	0	
0	0	0	0	0*					
for shooting pain score					0	100	80		
20	0	0	0	0	0*				
numbness score					0	0	0	0	
0	0	0	0	0					
electric pain score					0	0	0		
0	0	0	0	0	0				
tingling pain score					50	20	0		
0	0	0	0	0	0*				
squeezing pain score					0	0	0		
0	0	0	0	0	0				
freezing pain score					0	0	0		
0	0	0	0	0	0				
unpleasant pain score					70	100	95		
75	60	80	60	50	45*				
overwhelming pain score					95	90	70		
50	30	25	40	20	20*				
score for increased pain due to touch					0	0	0		
0	0	0	0	0	0				
score for increased pain due to weather changes					0	0	0		
0	0	0	0	0	0				
AVERAGE PAIN LAST 24 HOURS					5	8	5		
8	8	8	4	3	4*				
LEAST PAIN LAST 24 HRS					0	0	0		
0	0	2	2	0	1				
PAIN SCORE RIGHT NOW					5	4	6		
8	2.5	5	6	5	7				
WORST PAIN SCORE LAST 24 HOURS					10	10	8		
8	8	9	7	5	7*				
PERCENTAGE PAIN RELIEF LAST					10	10	15		
15	75	65	50	75	75*				
24 HOURS									

SCORE GENERAL ACTIVITY 8 8 6 5
5. . .
DETD . . . 1, 2, 3. Wherein animals that were injected with either 3+10.sup.3 or 3+10.sup.4 syngeneic MRMT-1 cells who were treated with flupirtine and morphine showed, when compared to either control animals or animals treated with saline.
DETD Central pain models are used to test the analgesic effects of flupirtine both with and without morphine. The majority of central pain models are based on spinal cord injury (SCI). Dysesthesia is. . .
DETD . . . to such surgery typically self attack and mutilate the denervated limb. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . last for the entire duration of the study (over 2 months). The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . the injury side. The evoked pain can develop into bilateral patterns. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . lifting of ipsilateral hind paw), autotomy is absent in the SNL. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . to L5 ligation and exhibit long lasting hyperalgesia and mechanical allodynia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . induces autotomy and touch allodynia which lasts 15 to 21 days. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . develop within a day after injury, and can last for weeks. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD . . . nerve. In this model allodynia is seen hours after the injection. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .
DETD Rats are injected with either vinca alkaloids, platinum compounds or Taxols or other chemotherapeutic agents also capable of inducing neuropathy. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold or paw flick latency.

DETD . . . drug-free days+5 more drug days) resulting in the production of hyperalgesia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . vincristine infusion so as to induce in a dose-dependent tactile allodynia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . by the vinca alkaloids) and blocks polymerization of microtubules. Its effectiveness is limited by the development of severe painful peripheral neuropathy that is dose-dependent. The incidence of Taxol neuropathy is estimated to be 50-90%, and is characterised by dysesthesia (e.g. numbness, tingling and burning pain) of the hands and feet. Rats are injected with Taxol resulting in neuropathic pain. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw withdrawal threshold or paw flick latency.

DETD . . . daily injections (i.p.) of cisplatin which produces mechanical allodynia and hyperalgesia. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . the nerve. Signs of spontaneous pain (paw lifting) are also visible. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . markers occur within 14 days, and can be attenuated by osteoprotegerin. The mice are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . 6 days after implantation and last for at least 16 days. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

DETD . . . cell number)-dependent, and occur within 10-12 days of tumor cell injection. The rats are then divided into three groups: 1) flupirtine alone; 2) flupirtine and morphine; and 3) saline. The animals are then monitored using standard behavioural tests for pain, such as the paw. . .

CLM What is claimed is:

43. A method for inducing an analgesic response to neuropathic pain in a mammal, said method comprising administering to the mammal, a composition comprising the structure ##STR1## or a pharmaceutically acceptable salt thereof in combination with an opioid selected from the list consisting of fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, desomorphine, apomorphine, diamorphine, pethidine, methadone, dextropropoxyphene,. . . homologs or analogs thereof, in an amount effective to reduce the level of or to otherwise ameliorate the sensation of pain.

CLM What is claimed is:
44. The method of claim 43 further comprising the administration of the opioid concurrently or sequentially to the flupirtine.

CLM What is claimed is:
45. The method of claim 44 wherein the opioid is morphine, fentanyl, oxycodone or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:
46. The method of any one of claims 43 to 45 wherein the opioid does not induce overt sedation in the presence of flupirtine.

CLM What is claimed is:
47. The method of claim 43 wherein flupirtine is administered in an amount of about 0.5 mg/kg to about 20 mg/kg of body weight.

IT 57-27-2, Morphine, biological studies 56995-20-1, Flupirtine (flupirtine compns. for treatment of neuropathic or inflammatory pain treatment)

L9 ANSWER 5 OF 40 IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

ACCESSION NUMBER: 2007:5365 IMSDRUGNEWS
TITLE: CNSB 001 CNSBio phase change II, Australia(neuropathic pain) CNSBio clinical data (phase II)(neuropathic pain)
SOURCE: R&D Focus Drug News (26 Nov 2007).
WORD COUNT: 118
TI CNSB 001 CNSBio phase change II, Australia(neuropathic pain) CNSBio clinical data (phase II)(neuropathic pain)
TX CNSBio is developing CNSB 001, a fixed combination of the potassium channel opener flupirtine and an opioid drug for the treatment of neuropathic pain. A phase IIa, multidose, proof-of-concept, placebo-controlled trial is under way in Australia for the treatment of neuropathic pain in HIV patients.
Interim results show that there is statistically significant improvement in average pain and quality of life. This information was disclosed at BIO-Europe 2007, 12-14 November 2007, Hamburg, Germany. Phase I/IIa open-label trials in cancer patients with significant neuropathic pain have been completed. Results showed the product to have high tolerability and efficacy. CNSBio plans to initiate a dose titration, 12-week, open-label, phase IIa trial in patients with painful diabetic neuropathy in February 2008.

CN flupirtine + opioid; opioid + flupirtine; CNSB 001

CN flupirtine + opioid; opioid + flupirtine; CNSB 001

L9 ANSWER 6 OF 40 USPATFULL on STN DUPLICATE 1
ACCESSION NUMBER: 2007:49224 USPATFULL
TITLE: Sirtuin modulating compounds
INVENTOR(S): Nunes, Joseph J., Andover, MA, UNITED STATES
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PATENT ASSIGNEE(S): Sirtris Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070043050	A1	20070222
	US 7345178	B2	20080318
APPLICATION INFO.:	US 2006-499919	A1	20060804 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-705612P	20050804 (60)
	US 2005-741783P	20051202 (60)
	US 2006-779370P	20060303 (60)
	US 2006-792276P	20060414 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & NEAVE IP GROUP, ROPES & GRAY LLP, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624, US
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 15181
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . (such as edaravone, vitamin E, and vitamin C), glutamate antagonists, AMPA antagonists, kainate antagonists, NMDA antagonists, GABA agonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, Na.sup.+/Ca.sup.2+ channel inhibitory drugs, and K.sup.+ channel opening drugs. Examples of the brain metabolic stimulants. . .

DETD A less frequent, but more severe type of neuropathy is known as acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP). In AIDP/CIDP there is damage to the fatty membrane covering the nerve impulses. This kind of neuropathy involves inflammation and resembles the muscle deterioration often identified with long-term use of AZT. It can be the first manifestation of HIV infection, where the patient may not complain of pain, but fails to respond to standard reflex tests. This kind of neuropathy may be associated with seroconversion, in which case it can sometimes resolve spontaneously. It can serve as a sign of. . .

DETD Diabetic neuropathies are neuropathic disorders that are associated with diabetes mellitus. These conditions usually result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum). Relatively common conditions which may be associated with diabetic neuropathy include third nerve palsy; mononeuropathy; mononeuritis multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy. Clinical manifestations of diabetic neuropathy include, for example, sensorimotor polyneuropathy such as numbness, sensory loss, dysesthesia and nighttime pain; autonomic neuropathy such as delayed gastric emptying or gastroparesis; and cranial neuropathy such as

oculomotor (3rd) neuropathies or Mononeuropathies of the thoracic or lumbar spinal nerves.

DETD Other PNS diseases treatable with sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include: Brachial Plexus Neuropathies (diseases of the cervical and first thoracic roots, nerve trunks, cords, and peripheral nerve components of the brachial plexus. Clinical manifestations include regional pain, paresthesia; muscle weakness, and decreased sensation in the upper extremity. These disorders may be associated with trauma, including birth injuries;. . . thoracic outlet syndrome; neoplasms, neuritis, radiotherapy; and other conditions. See Adams et al., Principles of Neurology, 6th ed, pp1351-2); Diabetic Neuropathies (peripheral, autonomic, and cranial nerve disorders that are associated with diabetes mellitus). These conditions usually result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum). Relatively common conditions which may be associated with diabetic neuropathy include third nerve palsy; mononeuropathy; mononeuritis multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy (see Adams et al., Principles of Neurology, 6th ed, p1325); mononeuropathies (disease or trauma involving a single peripheral nerve in. . . of causes, including ischemia; traumatic injury; compression; connective tissue diseases; cumulative trauma disorders; and other conditions; Neuralgia (intense or aching pain that occurs along the course or distribution of a peripheral or cranial nerve); Peripheral Nervous System Neoplasms (neoplasms which arise. . . a direct mechanical effect; Neuritis (a general term indicating inflammation of a peripheral or cranial nerve). Clinical manifestation may include pain; paresthesias; paresis; or hyperesthesia; Polyneuropathies (diseases of multiple peripheral nerves). The various forms are categorized by the type of nerve. . .

DETD . . . result of treatment with vincristine and many will experience some degree of tingling (paresthesia) in their fingers and toes. The neuropathy does not usually manifest itself right at the start of the treatment but generally comes on over a period of. . . a few weeks. It is not essential to stop the drug at the first onset of symptoms, but if the neuropathy progresses this may be necessary. It is very important that patients should report such symptoms to their doctors, as the. . . such as vinblastine or vindesine if the symptoms are mild. Occasionally, the nerves supplying the bowel are affected causing abdominal pain and constipation.

DETD Exemplary potassium channel openers include diazoxide, flupirtine, pinacidil, levcromakalim, rilmakalim, chromakalim, PCO-400 and SKP-450 (2-[2"(1",3"-dioxolone)-2-methyl]-4-(2'-oxo-1'-pyrrolidinyl)-6-nitro-2H-1-benzopyra-n).

DETD . . . floctafenine, fluazacort, flucloronide, flufenamic acid, flumethasone, flunisolide, flunixin, flunoxaprofen, fluocinolone acetonide, fluocinonide, fluocinolone acetonide, fluocortin butyl, fluocortolone, fluoresone, fluorometholone, fluperolone, flupirtine, fluprednidene, fluprednisolone, fluproquazone, flurandrenolide, flurbiprofen, fluticasone, formocortal, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, halcinonide, halobetasol, halometasone, haloprednone, heroin,. . .

DETD . . . symptom associated with a disease or disorder involving mitochondrial dysfunction (such as, an anti-seizure agent, an agent

useful for alleviating neuropathic pain, an agent for treating cardiac dysfunction), a cardiovascular agent (as described further below), a chemotherapeutic agent (as described further below),. . .

L9 ANSWER 7 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2007:342101 USPATFULL		
TITLE:	Analgesic		
INVENTOR(S):	Izumimoto, Naoki, Kanagawa, JAPAN Kawamura, Kuniaki, Kanagawa, JAPAN Komagata, Toshikazu, Kanagawa, JAPAN Hashimoto, Tadatoshi, Osaka, JAPAN Nagabukuro, Hiroshi, Osaka, JAPAN		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070299100	A1	20071227
APPLICATION INFO.:	US 2005-667136	A1	20051104 (11)
	WO 2005-JP20297		20051104
			20070504 PCT 371 date
	NUMBER	DATE	
PRIORITY INFORMATION:	JP 2004-320583	20041104	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	IP GROUP OF DLA PIPER US LLP, ONE LIBERTY PLACE, 1650 MARKET ST, SUITE 4900, PHILADELPHIA, PA, 19103, US		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	8 Drawing Page(s)		
LINE COUNT:	1621		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Causes of pain are known to include the cases where a tissue is damaged by a disease or injury so that an algesic substance is topically produced, and the cases wherein there is no direct factor such as noxious stimulus, but the pain is caused by dysfunction of nerve system or the like. Pain may be largely classified into 3 groups depending on the cause, that is, (1) nociceptive pain , (2) neuropathic pain and (3) psychogenic pain. The "nociceptive pain" is the pain caused by an external stimulus such as injury and the pain caused by a lesion in an internal tissue. Most of this type of pain is transient, which disappears when the underlying disease is cured, so that it is usually classified into acute pain. On the other hand, chronic pain is caused by dysfunction of central nervous system due to abnormality of a peripheral tissue or terminal portion of peripheral. . . or due to damage of peripheral nerve, or caused by damage of central nervous system or psychologic mechanism. The above-mentioned neuropathic pain and the psychogenic pain belong to this chronic pain. Although pain is caused by various factors and its expression mechanism has not been well understood, reported endogenous substances related to pain and its regulation include bradykinin, histamine, prostaglandin, serotonin, substance P and opioid peptides.

SUMM As the therapeutic drugs against mild pain, nonsteroidal

anti-inflammatory drugs (NSAIDs) such as aspirin and acetaminophen, having a site of action in the periphery have been used. As the therapeutic drugs against moderate or severe pain, opioid analgesics typified by morphine, having a site of action in the central nervous system have been used. However, the peripheral. . . . effect against digestive, in addition to the fact that the analgesic effects thereof are not sufficient in some cases. The opioid analgesics have a problem in that they have side effects such as nausea, vomiting, constipation and dependence. Further, although the analgesics typified by morphine exhibit effects against acute pain, they do not exhibit sufficient effects against neuropathic pain and psychogenic pain in most cases. Thus, creation of a novel analgesic which is not only effective against acute pain, but also effective against the chronic pain for which morphine is not effective, of which side effect is small, is demanded.

SUMM The pain which is treated by the analgesic includes neuropathic pain, diabetic neuralgia and chronic pelvic visceral pain. We further provide a method for relieving or allaying pain, comprising administering an effective amount of one or more of the above-described morphinan derivatives having a nitrogen-containing heterocyclic group and. . . .

DRWD FIG. 8 shows the results of the experiment for confirming the analgesic activity of Compound 10f, by the diabetic induced neuropathic pain model method. Each group consisted of 4 rats (n=4). ***: P<0.001, **: P<0.01, *P<0.05 vs. vehicle-treated group (multiple paired t. . . .

DETD . . . nitrogen-containing heterocyclic group represented by Formula (I) and the pharmaceutically acid addition salts thereof are effective for the therapy of pain may be confirmed by showing the actions of the compounds to reduce the behavior induced by pain in animal models. For example, the reported testing methods utilizing the behavior induced by pain in animal models include mouse acetic acid writhing method (Life Sci., vol 65, 1685-93 (1996)) for treating acute pain, PGF.sub.2α-induced allodynia model method in which pain is induced, for which morphine is ineffective (Pain. Vol 50, 223-229 (1992)), rat Chung model method (Pain. Vol 50, 355-363 (1992)), mouse Seltzer model method (Pain. Vol 76, 215-222 (1998)) and diabetic induced neuropathic pain model method (Pain. Vol 80, 391-398)). PGF.sub.2α-induced allodynia model has also been reported as an animal model which induces allodynia that is a characteristic symptom to the patients suffering from chronic pain (PAIN RESEARCH., vol 7, 129-134 (1992), Pain. Vol 50, 223-229 (1992)).

DETD . . . it was confirmed that they have analgesic activities in PGF.sub.2α-induced allodynia model, rat Chung model, mouse Seltzer model, diabetic induced neuropathic pain model, and in evaluation of activity to relieve cystalgia caused by hyperextension of bladder using myoelectric activity of external oblique abdominal muscle as index, so that the derivatives may be widely applied to various pain ranging from acute pain to chronic pain. The analgesic may be applied to acute pain including, for example, pain due to injuries such as fracture and incised wound; pain due to inflammation such as appendicitis; and postoperative pain; and to chronic pain including neuropathic pain such as

cancer pain, herpes zoster pain, postherpetic neuralgia, trigeminal neuralgia; and pain due to diabetic neuralgia, causalgia, phantom limb pain. In addition, they may be applied to deep pain and visceral pain such as headache, abdominal pain, back pain, chronic pelvic pain syndrome, cystalgia, pain due to vaginitis, (chronic) prostatitis, endometriosis, myoma of the uterus, urolithiasis, urethral calculus, cystitis, urethritis, urinary tract infection or due to interstitial cystitis, colicky pain due to digestive organ disease, pelvic pain, urologic diseases pain; and pain in gynecologic field such as pain due to dysmenorrhea; and psychogenic pain. The analgesic may be used for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey and human).

DETD . . . acid, ketoprofen, piroxicam, mefenamic acid, tiaramide, naproxen, Loxonin, oxaprozin, zaltoprofen, etodolac, meloxicam, lornoxicam, amproxicam, celecoxib, rofecoxib, valdecoxib, lumiracoxib and licofelone; opioid analgesics such as codeine, morphine, dihydrocodeine, hydrocodone, hydromorphone, oxycodone, fentanyl, buprenorphine, butorphanol, nalbuphine, pentazocine, levorphanol, methadone, pethidine, tramadol and oxymorphone;. . . vanilloid agonists and antagonists such as capsaicin and resiniferatoxin; calcium channel blockers such as ziconotide; potassium channel openers such as flupirtine and retigabine; serotonin receptor antagonists; sodium channel blockers; cannabinoids; and toxins such as botulinum toxin and tetrodotoxin, but these drugs. . .

CLM What is claimed is:

9. The analgesic according to claim 1 to 8, wherein the treating pain is neuropathic pain, diabetic neuralgia or chronic pelvic visceral pain.

L9 ANSWER 8 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2007:322595 USPATFULL
TITLE:	Anti-inflammatory and analgesic compositions and related methods
INVENTOR(S):	Tyavanagimatt, Shanthakumar, Salt Lake City, UT, UNITED STATES Fikstad, David, Salt Lake City, UT, UNITED STATES Giliyar, Chandrashekar, Salt Lake City, UT, UNITED STATES Patel, Mahesh, Salt Lake City, UT, UNITED STATES Venkateshwaran, Srinivasan, Salt Lake City, UT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070281927	A1	20071206
APPLICATION INFO.:	US 2006-448597	A1	20060606 (11)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	THORPE NORTH & WESTERN, LLP., 8180 SOUTH 700 EAST, SUITE 350, SANDY, UT, 84070, US
NUMBER OF CLAIMS:	75
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Page(s)
LINE COUNT:	1860

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . useful to provide adequate pain management for many individuals without producing many of the side effects and dependencies prevalent with opioid pain management.
DETD . . . 7.5 mg to 15 mg once daily. Meloxicam is known for the treatment of many indications, including without limitation acute pain and chronic pain from a wide variety of sources (nociceptive and neuropathic); osteoarthritis; rheumatoid arthritis; juvenile polyarticular arthritis; ankylosing spondylitis; migraine; amyotrophic lateral sclerosis; diabetes related ocular disorders; cardiovascular disorders, including acute coronary syndromes; polycystic kidney disease; cancer; preterm labor; prostatitis or pelvic pain syndrome; organ injury during transplantation; psychiatric disorders including schizophrenia, delusional disorders, affective disorders, autism or tic disorders; obesity; urinary incontinence;. . .
DETD . . . include nearly any useful active agent known to one of ordinary skill in the art. Examples include, without limitation, opioids, non-opioid analgesics such as ibuprofen, acetaminophen, aspirin, etc., cold or cough remedies, such as antihistamines, decongestants, expectorants, anti-tussives, 5-HT1 agonists, calcium. . .
DETD . . . a second active agent may be acidic, with pH-dependent solubility. In another aspect, a second active agent may include an opioid and/or another analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e., non-addictive) analgesics, monoamine uptake inhibitors, adenosine. . .
DETD . . . ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen,. . .
CLM What is claimed is:
. . . The method of claim 69, wherein the second active agent includes a member selected from the group consisting of opioids, non-opioid analgesics, antitussives, expectorants, antihistamines, decongestants, 5-HT1 agonists, calcium channel blockers, beta-adrenergic receptor blocking agents, xanthine derivatives, prostaglandin analogs, antacids, proton-pump. . .

L9 ANSWER 9 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2007:303296 USPATFULL
TITLE: (S)-N-methylnaltrexone
INVENTOR(S): Boyd, Thomas A., Grandview, NY, UNITED STATES
Wagoner, Howard, Warwick, NY, UNITED STATES
Sanghvi, Suketu P., Kendall Park, NJ, UNITED STATES
Verbicky, Christopher, Broadalbin, NY, UNITED STATES
Andruski, Stephen, Clifton Park, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070265293	A1	20071115	
APPLICATION INFO.:	US 2006-441452	A1	20060525	(11)

NUMBER DATE

PRIORITY INFORMATION:	US 2005-684570P 20050525 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WOLF GREENFIELD & SACKS, P.C., 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2206, US
NUMBER OF CLAIMS:	78
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Page(s)
LINE COUNT:	3572

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Methylnaltrexone (MNTX) is a quaternary derivative of the pure opioid antagonist, naltrexone. It exists as a salt. Names used for the bromide salt of MNTX in the literature include: Methylnaltrexone. . .

SUMM . . . and chemical properties. All of the reported functions of MNTX described in the literature indicate that MNTX is a peripheral opioid antagonist. Some of these antagonist functions are described in U.S. Pat. Nos. 4,176,186, 4,719,215, 4,861,781, 5,102,887, 5,972,954, 6,274,591, 6,559,158, and. . . gastric hypomotility, delayed gastric emptying and immune suppression. The art discloses that MNTX not only reduces the side-effects stemming from opioid analgesic treatment but also reduces the side-effects mediated by endogenous opioids alone or in conjunction with exogenous opioid treatment. Such side-effects include inhibition of gastrointestinal motility, post-operative gastrointestinal dysfunction, idiopathic constipation and other such conditions including, but not. . .

SUMM . . . protocol for obtaining S-MNTX was unpredictable from the prior art. In addition, it has been discovered, surprisingly, that S-MNTX has opioid agonist activity.

SUMM . . . embodiments, the pharmaceutical preparation further includes a therapeutic agent other than MNTX. In one embodiment, the therapeutic agent is an opioid or opioid agonist. Examples of opioids or opioid agonists are alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan,. . . nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, tramadol, or combinations thereof. In some embodiments, the opioid or opioid agonist does not readily cross the blood brain barrier and, therefore, has substantially no central nervous system (CNS) activity when. . . it is of the class of agents known as "peripherally acting") agents. In other embodiments the therapeutic agent is an opioid antagonist. Opioid antagonists include peripheral mu opioid antagonists. Examples of peripheral mu opioid antagonists include quartemary derivatives of noroxymorphone (See Goldberg et al, U.S. Pat. No. 4,176,186, and Cantrell et al WO 2004/043964),. . .

SUMM In one embodiment, the peripheral opioid antagonist is R-MNTX. R-MNTX is the predominant form of MNTX following the manufacturing procedures described in the prior art, although. . .

SUMM In other embodiments, the therapeutic agent is not an opioid, opioid agonist, or an opioid antagonist. For example, the therapeutic agent can be an antiviral agent, antibiotic agent, antifungal agent, antibacterial agent, antiseptic agent, anti-protozoal.

. .
SUMM . . . in time whereby both agents are treating the condition at the same time. In one embodiment, the agent is an opioid or an opioid agonist. In another embodiment, the agent is not an opioid or an opioid agonist.
SUMM . . . be administered in conjunction with another motility inhibiting agent that is not S-MNTX. In one embodiment, the agent is an opioid or an opioid agonist. Opioids and opioid agonists are described above. In another embodiment, the agent is not an opioid or an opioid agonist. Examples of such gastrointestinal motility inhibiting agents are described below, each as if recited specifically in this summary of. . .
SUMM . . . administering to the subject a therapeutic agent other than S-MNTX. In one embodiment the agent other than S-MNTX is an opioid. In another embodiment, the agent other than S-MNTX is a nonopioid pain relieving agent. Nonopioid pain relieving agents include corticosteroids. . .
SUMM . . . a patient in need of such treatment a pharmaceutical composition containing S-MNTX and administering to the subject a peripheral mu opioid antagonist, both in amounts to regulate gastrointestinal function. In one embodiment, the peripheral mu opioid antagonist is R-MNTX.
SUMM . . . further can include a therapeutic agent other than S-MNTX. The therapeutic agent other than S-MNTX in one embodiment is an opioid or opioid agonist. In one aspect, the opioid or opioid agonist has substantially no CNS activity when administered systemically (i.e., is "peripherally acting"). In other embodiments, the therapeutic agent other than S-MNTX is an opioid antagonist. Opioid antagonists include peripheral mu opioid antagonists. In one embodiment, the peripheral opioid antagonist is R-MNTX. In other embodiments, the agent other than S-MNTX is an antiviral agent, antibiotic agent, antifungal agent, antibacterial. . .
SUMM According to another aspect of the invention, methods are provided for ensuring the manufacture of S-MNTX (which is an opioid agonist) that is free of R-MNTX (which is an opioid antagonist). The methods permit for the first time the assurance that a pharmaceutical preparation of S-MNTX which is intended for. . .
DETD . . . R-MNTX or mixtures of R-MNTX and S-MNTX. As discovered and claimed herein, pure S-MNTX behaves as an agonist of peripheral opioid receptors as demonstrated by inhibition of gastrointestinal transit. As a consequence, S-MNTX activity may be interfered with or antagonized by. . .
DETD . . . particularly useful in reverse phase HPLC chromatography. The S-MNTX of the present invention by virtue of its agonist activity on opioid receptors, is useful as a standard of agonist activity in in vitro and in vivo opioid receptor assays such as those described herein.
DETD The S-MNTX can be used to regulate a condition mediated by one or more peripheral opioid receptors, prophylactically or therapeutically, to agonize peripheral opioid receptors, in particular peripheral mu opioid receptors. The subjects being administered S-MNTX may receive treatment acutely, chronically or on an as needed basis.
DETD Mu and other opioid receptors exist in the gastrointestinal tract. Of the major classes of opioid receptors in the GI

tract, mu receptors are principally involved in modulation of GI activity. Kappa opioid receptors may play a role (Manara L et al Ann. Rev. Phamacol. Toxicol, 1985, 25:249-73). In general, the S-MNTX is used to prevent or treat conditions associated with the need for activation or modulation of opioid receptors, in particular, peripheral opioid receptors. Of interest is the use of S-MNTX to prevent or treat conditions associated with the need for activation or modulation of opioid receptors in the GI tract, in particular mu opioid receptors. Such conditions which may be prevented or treated include diarrhea and used to prevent or inhibit certain forms of. . .

DETD . . . aspect, S-MNTX can be used to treat diarrhea. Gastrointestinal function is regulated, at least in part, by one or more opioid receptors as well as endogenous opioids. Opioid antagonists are known to increase gastrointestinal motility and may thus be used effectively as a treatment for constipation. Opioid agonists on the other hand, in particular peripheral opioid agonists such as loperamide are known to decrease gastrointestinal motility and can be useful in treating diarrhea in mammals. S-MNTX as discovered by Applicants as an opioid agonist, can be administered to a patient in need of treatment for diarrhea. Diarrhea as used herein is defined as. . .

DETD The S-MNTX of the present invention by virtue of its opioid agonist activity is useful in the prevention and treatment of diarrhea having diverse etiology including acute and chronic forms of. . .

DETD . . . be administered in conjunction with another motility inhibiting agent that is not S-MNTX. In one embodiment, the agent is an opioid or an opioid agonist. Opioids and opioid agonists are described above. In another embodiment, the agent is not an opioid or an opioid agonist. Examples of such nonopioid gastrointestinal motility inhibiting agents include, for example, cisapride, antacids, aluminum hydroxide, magnesium aluminum silicate, magnesium. . .

DETD . . . animal's response to a strong stimulus without obtunding general behavior or motor function are referred to as analgesics. Opiates and opioid agonists affect pain via interaction with specific opioid receptors. Given the discovery that S-MNTX has opiate agonist activity on gastrointestinal transit in rats, there is a rationale for. . .

DETD In general, pain can be nociceptive, somatogenic, neurogenic, or psychogenic. Somatogenic pain can be muscular or skeletal (i.e., osteoarthritis, lumbosacral back pain, posttraumatic, myofascial), visceral (i.e., pancreatitis, ulcer, irritable bowel), ischemic (i.e., arteriosclerosis obliterans), or related to the progression of cancer (e.g., malignant or non-malignant). Neurogenic pain can be due to posttraumatic and postoperative neuralgia, can be related to neuropathies (i.e., diabetes, toxicity, etc.), and can be related to nerve entrapment, facial neuralgia, perineal neuralgia, postamputation, thalamic, causalgia, and reflex. . .

DETD Specific examples of conditions, diseases, disorders, and origins of pain amenable to management according to the present invention include, but are not necessarily limited to, cancer pain (e.g., metastasis or non-metastatic cancer), inflammatory disease pain, neuropathic pain, postoperative pain, iatrogenic pain (e.g., pain following invasive procedures or high dose radiation therapy, e.g., involving scar

tissue formation resulting in a debilitating compromise of freedom of motion and substantial pain), complex regional pain syndromes, failed-back pain (e.g., acute or chronic back pain), soft tissue pain, joints and bone pain , central pain, injury (e.g., debilitating injuries, e.g., paraplegia, quadriplegia, etc., as well as non-debilitating injury (e.g., to back, neck, spine, joints, legs, arms, hands, feet, etc.)), arthritic pain (e.g., rheumatoid arthritis, osteoarthritis, arthritic symptoms of unknown etiology, etc.), hereditary disease (e.g., sickle cell anemia), infectious disease and resulting. . . syndromes (e.g., Lyme disease, AIDS, etc.), headaches (e.g., migraines), causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, denervation, and the like. Pain can be associated with any portion(s) of the body, e.g., the musculoskeletal system, visceral organs, skin, nervous system, etc.

DETD The methods of the invention can be used to manage pain in patients who are opioid naive or who are no longer opioid naive. Exemplary opioid naive patients are those who have not received long-term opioid therapy for pain management. Exemplary non-opioid naive patients are those who have received short-term or long-term opioid therapy and have developed tolerance, dependence, or other undesirable side effect. For example, patients who have intractable adverse side effects with oral, intravenous, or intrathecal morphine, transdermal fentanyl patches, or conventionally administered subcutaneous infusions of fentanyl, morphine or other opioid can achieve good analgesia and maintain favorable side-effects profiles with deliver of S-MNTX and derivatives thereof.

DETD . . . including but not limited, therapeutic agents that are pain relieving agents. In one embodiment, the pain relieving agent is an opioid or opioid agonist. In another embodiment, the pain relieving agent is a nonopioid pain relieving agent such as a corticosteroid or a. . . Drinidene; Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone; Fluradoline Hydrochloride; Flurbiprofen; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride;. . .

DETD . . . production and it is believed that a decrease in TNF production will result in a reduction in inflammation. Peripherally acting opioid agonists have been shown to decrease TNF production (U.S. Pat. No. 6,190,691). The peripherally selective k-opioid, asimadoline, has been shown to be a potent anti-arthritic agent in an adjuvant-induced arthritis animal model (Binder, W. and Walker, J. S. Br. J. Pharma 124:647-654). Thus the peripheral opioid agonist activity of S-MNTX and derivatives thereof provide for prevention and treatment of inflammatory conditions. While not being bound by. . .

DETD . . . together with the S-MNTX are opioids. It has been surprisingly found by Applicants that S-MNTX used in combination with the opioid, morphine results in an enhanced and apparently synergistic inhibition of gastrointestinal transit. Thus, the present invention provides pharmaceutical compositions comprising. . . one or more opioids. This will permit alteration of doses not previously obtainable. For example, where a lower dose of opioid is

desirable in treating certain peripherally mediated conditions this now is possible by combination with S-MNTX treatment.

DETD The opioid can be any pharmaceutically acceptable opioid. Common opioids are those selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin),. . .

DETD Depending on the desired effect to be achieved the opioid may be administered parenterally or other systemic route to affect both the central nervous system (CNS) and peripheral opioid receptors. The desired effect of the opioid in combination with S-MNTX may be prevention or treatment of diarrhea, prevention or treatment of pain from any cause or. . . treatment of peripheral hyperalgesia. When the indication is prevention or treatment of peripheral hyperalgesia, it is desirable to provide an opioid which does not have concomitant CNS effects or alternatively to administer the opioid topically or locally such that the opioid does not substantially cross the blood brain barrier but provide an effect on peripheral opioid receptors.

DETD . . . e.g., U.S. Pat. No. 4,430,327; Burkhart et al. (1982) Peptides 3-869-871; Frederickson et al. (1991) Science 211:603-605] and other synthetic opioid peptides, such as H-Tyr-D-Nva-Phe-Orn-NH.sub.2, H-Tyr-D-Nle-Phe-Om-NH.sub.2, H-Tyr-D-Arg-Phe-A.sub.2bu-NH.sub.2, H-Tyr-D-Arg-Phe-Lys-NH.sub.2, and H-Lys-Tyr-D-Arg-Phe-Lys-NH.sub.2 [see, U.S. Pat. No. 5,312,899; see, also Gesellchen et al. (1981). . .

DETD . . . can be configured as an oral dosage. The oral dosage may be a liquid, a semisolid or a solid. An opioid may optionally be included in the oral dosage. The oral dosage may be configured to release the therapeutic agent(s) of the invention before, after or simultaneously with the other agent (and/or the opioid). The oral dosage may be configured to have the therapeutic agent(s) of the invention and the other agents release completely. . .

DETD FIG. 7 shows a kit according to the invention. The kit 10 includes a vial 12 containing opioid tablets. The kit 10 also includes a vial 14 containing S-MNTX tablets which comprise pellets, some of which are enterically. . .

DETD S-MNTX was shown to bind human recombinant mu opioid receptors with a Ki=0.198 μM; to bind human recombinant kappa opioid receptors with Ki=1.76 μM, and did not bind to human recombinant delta opioid receptors.

DETD . . . (10 μM) and GR113808 (0.1 μM) were also present throughout the experiments to prevent prostanoid release and to block the k-opioid, 5-HT2, 5-HT3 and 5-HT4 receptors, respectively. The tissues were connected to force transducers for isometric tension recordings. They were stretched. . .

DETD Results. The effects of S-MNTX investigated from 1.0E-08 M to 1.0E-04 M for agonist and antagonist activities at the μ- opioid receptors in the guinea pig ileum bioassay are presented in Table IV.1 where those of the reference compounds are also. . .

DETD These results indicate that S-MNTX behaves as an agonist at the μ-opioid receptors in this tissue.

TABLE IV.1

Effects of S-MNTX evaluated for agonist and antagonist activities at the μ-opioid receptors in the guinea pig ileum

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Evaluation of agonist activity

Compounds	Control response to DAMGO +naloxone (1.0E-07. . .	Responses to increasing concentrations

DETD
TABLE IV.2

EC.sub.50 and IC.sub.50 values determined for S-MNTX at the μ- opioid receptors in the guinea pig ileum

Compound	Agonist activity EC.sub.50 value	Antagonist activity IC.sub.50 value
S-MNTX	2.0E-06 M	No antagonist. . .

DETD The results from the GI transit study are shown in Table 1. Morphine, known to affect both central and peripheral opioid receptors, decreased GI motility as reported in the literature. R-MNTX, a peripherally selective mu opioid receptor antagonist, had no effect on GI transit when administered alone. R-MNTX administered prior to morphine reversed the GI slowing effect of morphine as would be expected from an opioid antagonist. The antagonist activity of R-MNTX on morphine was dose-dependent, with a partial reversal at 1 mg/kg and reversal at. . .

DETD The mu opioid receptor is G.sub.i coupled, which works by inhibiting a cAMP increase. Thus in these experiments, cellular cAMP was increased by. . .

DETD . . . CTOP, naloxone and ciprodime inhibited the cAMP inhibition. Thus full antagonist effect was equivalent to forskolin without any addition of μ- opioid agonist. In these experiments, antagonist was added, then 30 μM DAMGO, then forskolin. Therefore, increasing antagonist concentration increased cAMP.

CLM What is claimed is:
29. The pharmaceutical composition of claim 28, wherein the therapeutic agent is an opioid or opioid agonist.

CLM What is claimed is:
32. The pharmaceutical composition of claim 28, wherein the therapeutic agent is not an opioid, opioid agonist, or an opioid antagonist.

CLM What is claimed is:
86. The kit according to claim 85, wherein the therapeutic agent is an opioid or opioid agonist.

CLM What is claimed is:
87. The kit according to claim 86, wherein the opioid or opioid agonist has substantially no CNS activity.

CLM What is claimed is:
89. The kit according to claim 85, wherein the therapeutic agent is a peripheral opioid antagonist.

CLM What is claimed is:
90. The kit according to claim 89, wherein the peripheral opioid

antagonist is R-MNTX.

CLM What is claimed is:
91. The kit according to claim 89, wherein the peripheral opioid antagonist is a piperidine N-alkylcarboxylate, a quartemary derivative of noroxymorphone, an opium alkaloid derivative, or a quarternary benzomorphan.

CLM What is claimed is:
. . . regulating gastrointestinal function comprising administering to a subject in need thereof S-MNTX, and administering to the subject a peripheral mu opioid antagonist.

L9 ANSWER 10 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2007:291241 USPATFULL
TITLE: 1,5 And 3,6- substituted indole compounds having NOS inhibitory activity
INVENTOR(S): Maddaford, Shawn, Mississauga, CANADA
Ramnauth, Jailall, Brampton, CANADA
Rakhit, Suman, Mississauga, CANADA
Patman, Joanne, Mississauga, CANADA
Renton, Paul, Toronto, CANADA
Annedi, Subhash C., Mississauga, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070254940	A1	20071101
APPLICATION INFO.:	US 2007-787167	A1	20070413 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-791846P	20060413 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110, US
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5216
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . for example, stroke, reperfusion injury, neurodegeneration, head trauma, CABG, migraine headache with and without aura, migraine with allodynia, central post-stroke pain (CPSP), neuropathic pain, or chronic pain.
SUMM . . . artery bypass graft (CABG) associated neurological damage, migraine with and without aura, migraine with allodynia, chronic tension type headache (CTTH), neuropathic pain, central post-stroke pain (CPSP), and chronic pain.
SUMM . . . the invention to the mammal. Examples of conditions that can be prevented or treated include migraine headache, migraine with allodynia, neuropathic pain, central post-stroke pain (CPSP), chronic tension type headache, chronic pain , acute spinal cord injury, diabetic nephropathy, an inflammatory disease, stroke, reperfusion injury, head trauma, cardiogenic shock, CABG associated neurological damage, HCA, AIDS associated dementia,

neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactive disorder, or psychosis.. . . stroke, reperfusion injury, neurodegeneration, head trauma, CABG, migraine headache with and without aura, migraine with allodynia, chronic tension type headache, neuropathic pain, central post-stroke pain (CPSP), morphine/opioid induced hyperalgesia or chronic pain. In particular, 1,5-substituted indole compounds are useful in the treatment of central post-stroke pain (CPSP).

SUMM . . . vanilloid VR1 receptor agonists, cannabinoid CB1/CB2 agonists, AMPA receptor antagonists, kainate receptor antagonists, sodium channel blockers (e.g., Nav1.8 blocker for neuropathic pain), nicotinic acetylcholine receptor agonists, a K.sub.ATP potassium channel, K.sub.v1.4 potassium channel, Ca.sup.2+-activated potassium channel, SK potassium channel, BK potassium channel,. . . muscarinic M1 agonists, muscarinic M2/M3 partial agonists/antagonists, and antioxidants.

TABLE 1

Therapeutic agents useful in combination with compounds of the invention

Class	Examples
Opioid	alfentanil, butorphanol, buprenorphine, codeine, dextromoramide, dextropropoxyphene, dezocine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, levorphanol, levomethadone, methadone, meptazinol, morphine, morphine-6-glucuronide,. . . setiptiline, sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, trazodone, tofenacin, tofisopam, toloxatone, tomoxetine, veralipride, viloxazine, viqualine, zimelidine, zometapine
Antiepileptic	carbamazepine, flupirtine, gabapentin, lamotrigine, oxcarbazepine, phenyloin, pregabalin, retigabine, topiramate, or valproate
Nonsteroidal anti-	acemetacin, aspirin, celecoxib, deracoxib, diclofenac, diflunisal, ethenzamide, etofenamate, etoricoxib, fenoprofen, flufenamic. . .

DRWD . . . of the experimental designs used in the Chung Spinal Nerve Ligation (SNL) model assays (tactile allodynia and thermal hyperalgesia) for neuropathic pain.

DRWD . . . mg/kg i.p. administration of compound 107 on the reversal of thermal hyperalgesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

DETD . . . artery bypass graft (CABG) associated neurological damage, migraine with and without aura, migraine with allodynia, chronic tension type headache (CTTH), neuropathic pain, central post-stroke pain (CPSP), chronic pain, prevention or reduction of opioid-induced hyperalgesia, opioid

induced tolerance and withdrawal, and chemical dependencies and addictions. Exemplary compounds of the invention are shown in Table 2.

TABLE. . .

DETD . . . a cell or animal in need thereof. Such diseases or conditions include, for example, migraine headache with and without aura, neuropathic pain, chronic tension type headache, chronic pain, acute spinal cord injury, diabetic neuropathy, diabetic nephropathy, an inflammatory disease, stroke, reperfusion injury, head trauma, cardiogenic shock, CABG associated neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactivity disorder, central post-stroke pain (CPSP), and psychosis.

DETD Acute Spinal Cord Injury, Chronic or Neuropathic Pain

DETD In humans, NO evokes pain on intracutaneous injection (Holthusen and Arndt, Neurosci. Lett. 165:71-74, 1994), thus showing a direct involvement of NO in pain. Furthermore, NOS inhibitors have little or no effect on nociceptive transmission under normal conditions (Meller and Gebhart, Pain 52:127-136, 1993). NO is involved in the transmission and modulation of nociceptive information at the periphery, spinal cord and supraspinal. . . 1992; Haley et al., Neuroscience 31:251-258, 1992). Lesions or dysfunctions in the CNS may lead to the development of chronic pain symptoms, known as central pain, and includes spontaneous pain, hyperalgesia, and mechanical and cold allodynia (Pagni, Textbook of Pain, Churchill Livingstone, Edinburgh, 1989, pp. 634-655; Tasker In: The Management of Pain, pp. 264-283, J. J. Bonica (Ed.), Lea and Febiger, Philadelphia, Pa., 1990; Casey, Pain and Central Nervous System Disease: The Central Pain Syndromes, pp. 1-11 K. L. Casey (Ed.), Raven Press, New York, 1991). It has been demonstrated that systemic administration (i.p.). . . of the NOS inhibitors 7-NI and L-NAME relieve chronic allodynia-like symptoms in rats with spinal cord injury (Hao and Xu, Pain 66:313-319, 1996). The effects of 7-NI were not associated with a significant sedative effect and were reversed by L-arginine (NO. . . (Neuroscience 50(1):7-10, 1992). Thus the NOS inhibitors of the present invention may be useful for the treatment of chronic or neuropathic pain.

DETD . . . an NOS inhibitor and N-methyl-D-aspartate (NMDA) channel antagonist. Agmatine is effective in both the spinal nerve ligation (SNL) model of neuropathic pain as well as the streptozotocin model of diabetic neuropathy (Karadag et al., Neurosci. Lett. 339(1):88-90, 2003). Thus compounds possessing NOS inhibitory activity, such as, for example, a compound of formula I, a combination of an NOS inhibitor and an NMDA antagonist should be effective in treating diabetic neuropathy and other neuropathic pain conditions.

DETD (b) Morphine/Opioid Induced Tolerance and Withdrawal Symptoms

DETD There is much evidence supporting the role of both the NMDA and NO pathways in opioid dependence in adult and infant animals. Adult or neonatal rodents injected with morphine sulfate develop behavioral withdrawal after precipitation with. . .

DETD Opioid-NOS Inhibitor Combinations in Chronic,

Neuropathic Pain

DETD Nerve injury can lead to abnormal pain states known as neuropathic pain. Some of the clinical symptoms include tactile allodynia (nociceptive responses to normally innocuous mechanical stimuli), hyperalgesia (augmented pain intensity in response to normally painful stimuli), and spontaneous pain. Spinal nerve ligation (SNL) in rats is an animal model of neuropathic pain that produces spontaneous pain, allodynia, and hyperalgesia, analogous to the clinical symptoms observed in human patients (Kim and Chung, Pain 50:355-363, 1992; Seltzer, Neurosciences 7:211-219, 1995).

DETD Neuropathic pain can be particularly insensitive to opioid treatment (Benedetti et al., Pain 74:205-211, 1998) and is still considered to be relatively refractory to opioid analgesics (MacFarlane et al., Pharmacol. Ther. 75:1-19, 1997; Watson, Clin. J Pain 16:S49-S55, 2000). While dose escalation can overcome reduced opioid effectiveness, it is limited by increased side effects and tolerance. Morphine administration is known to activate the NOS system, which. . . in the tail-flick or paw pressure models using coadministration of L-NAME or 7-NI with either a mu-, delta-, or kappa-selective opioid agonist (Machelska et al., J. Pharmacol. Exp. Ther. 282:977-984, 1997).

DETD . . . moderate to severe pain, in addition to the usual side effects that limit their utility, the somewhat paradoxical appearance of opioid-induced hyperalgesia may actually render patients more sensitive to pain and potentially aggravate their pain (Angst and Clark, Anesthesiology, 2006, 104(3), 570-587; Chu et. al. J. Pain 2006, 7(1) 43-48). The development of tolerance and opioid induced hyperalgesia is consistent with increased levels of NO production in the brain. The reduced analgesic response to opioids is. . .

DETD Thus, the combination of an nNOS inhibitor with an opioid (for example, those combinations described above) can enhance opioid analgesia in neuropathic pain and prevent the development of opioid tolerance and opioid -induced hyperalgesia.

DETD Antidepressant-NOS Inhibitor Combinations for Chronic Pain, Neuropathic Pain, Chronic Headache or Migraine

DETD Many antidepressants are used for the treatment of neuropathic pain (McQuay et al., Pain 68:217-227, 1996) and migraine (Tomkins et al., Am. J. Med. 111:54-63, 2001), and act via the serotonergic or noradrenergic system.. . . Res. 959:128-134, 2003). It is likely that NO is important in the mechanism by which antidepressants are effective for treating pain and depression, and that a combination of an nNOS inhibitor with an antidepressant, such as, for example, those combinations described. . .

DETD . . . other types of treatment (which may or may not inhibit NOS) to treat, prevent, and/or reduce the risk of stroke, neuropathic or migraine pain, or other disorders that benefit from NOS inhibition. In combination treatments, the dosages of one or more of the therapeutic. . .

DETD Efficacy in Models Predictive of Neuropathic-Like Pain States

DETD The efficacy of compound 107 for the treatment of neuropathic pain was assessed using standard animal models predictive of anti-hyperalgesic and anti-allodynic activity induced by a variety of methods.

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DETD The Chung Model of Injury-Induced Neuropathic-Like Pain:

DETD The experimental designs for the Chung Spinal Nerve Ligation SNL Model assay for neuropathic pain are depicted in FIG. 1. Nerve ligation injury was performed according to the method described by Kim and Chung (Kim and Chung, Pain 50:355-363, 1992). This technique produces signs of neuropathic dysesthesias, including tactile allodynia, thermal hyperalgesia, and guarding of the affected paw. Rats were anesthetized with halothane and the vertebrae.
. .

CLM What is claimed is:
17. The method of claim 15, wherein said condition is migraine headache, migraine with allodynia, neuropathic pain, central post-stroke pain (CPSP), chronic tension type headache, chronic pain, acute spinal cord injury, diabetic nephropathy, an inflammatory disease, stroke, reperfusion injury, head trauma, cardiogenic shock, CABG associated neurological damage, HCA, AIDS associated dementia, neurotoxicity, Parkinson's disease, Alzheimer's disease, ALS, Huntington's disease, multiple sclerosis, metamphetamine-induced neurotoxicity, drug addiction, morphine/opioid induced tolerance, dependence, hyperalgesia or withdrawal, ethanol tolerance, dependence, or withdrawal, epilepsy, anxiety, depression, attention deficit hyperactive disorder, or psychosis.
. . .

CLM What is claimed is:
. . . stroke, reperfusion injury, neurodegeneration, head trauma, CABG, migraine headache with and without aura, migraine with allodynia, chronic tension type headache, neuropathic pain, central post-stroke pain (CPSP), morphine/opioid induced hyperalgesia or chronic pain.

CLM What is claimed is:
20. The method of claim 15, wherein said method further comprises administering to said mammal an opioid.

CLM What is claimed is:
21. The method of claim 20, wherein said opioid is alfentanil, butorphanol, buprenorphine, dextromoramide, dezocine, dextropropoxyphene, codeine, dihydrocodeine, diphenoxylate, etorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, loperamide, levorphanol, levomethadone, meperidine, meptazinol,. . .

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DICTIONARY FILE UPDATES: 2 SEP 2008 HIGHEST RN 1045894-64-1

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             0 CNSB
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L10   0 CNSB 001
                (CNSB(W)001)

=> s cnsboo1
L11   0 CNSBOO1

=> s cnsb
L12   0 CNSB

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                   ENTRY   SESSION
FULL ESTIMATED COST   22.44   151.94

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FILE 'NLDB' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'NUTRACEUT' ENTERED AT 16:32:13 ON 03 SEP 2008

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FILE 'PASCAL' ENTERED AT 16:32:13 ON 03 SEP 2008

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FILE 'PHARMAML' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'PHIC' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'PHIN' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'SCISEARCH' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'TOXCENTER' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'USGENE' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'USPATFULL' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'USPATOLD' ENTERED AT 16:32:13 ON 03 SEP 2008

FILE 'USPAT2' ENTERED AT 16:32:13 ON 03 SEP 2008

=> d l9 21-30

L9 ANSWER 21 OF 40 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11309653 IFIPAT;IFIUDB;IFICDB
TI Substituted indole compounds having NOS inhibitory activity
IN Annedi Subhash C; Maddaford Shawn; Patman Joanne; Rakhit Suman; Ramnauth Jailall; Renton Paul
PA Unassigned Or Assigned To Individual (68000)
PPA NeurAxon Inc CA (Probable)
PI US 20060258721 A1 20061116
AI US 2006-404267 20060413
PRAI US 2005-670856P 20050413 (Provisional)
FI US 20060258721 20061116
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
OS CA 145:505332
ED Entered STN: 16 Nov 2006
    Last Updated on STN: 19 Dec 2006
CLMN 74

GI 23 Figure(s).

FIG. 1 is a bar graph showing the neuroprotective effect of compounds 9, 12, and 18 after NMDA challenge of rat cortical cells.

FIG. 2 is a bar graph showing the neuroprotective effect of compounds 9, 12, and 18 after challenge of oxygen-glucose-deprived (OGD) rat hippocampal slices.

FIG. 3 is a bar graph showing the effect of compound 12 on NMDA-mediated Ca2+ influx as measured using the fluorescent Ca2+ sensitive dye Fluo-4FF.

FIG. 4 is a graph showing the effects of compound 12 on NMDA-mediated whole-cell currents in rat cortical neurons.

FIG. 5 is a graph showing formalin-induced paw licking in mice after treatment with (a) vehicle, (b) compound 12 at 5 mg/kg and 10 mg/kg, (c) treatment with the non-selective inhibitor 7-nitroindazole (7-NI) at 2.5 mg/kg and 5 mg/kg.

FIG. 6 is a bar graph showing the dose-related effect of compound 12 on the string score evaluated 1 hour after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 7 is a bar graph showing the dose-related effect of compound 12 on the Hall score evaluated 1 hour after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 8 is a bar graph showing the dose-related effect of compound 12 on the string score evaluated 4 hours after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; *P<0.05 versus vehicle-treated injured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 9 is a bar graph showing the dose-related effect of compound 12 on the grip score evaluated 4 hours after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; *P<0.05 versus vehicle-treated injured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 10 is a bar graph showing the dose-related effect of compound 12 on the Hall score evaluated 4 hours after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; *P<0.05 versus vehicle-treated injured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 11 is a bar graph showing the dose-related effect of compound 12 on body temperature evaluated 1 hour after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 12 is a bar graph showing the dose-related effect of compound 12 on body temperature evaluated 4 hours after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger dagger dagger P<0.001 versus uninjured mice; *P<0.05 versus vehicle-treated injured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 13 is a bar graph showing the dose-related effect of compound 12 on body weight loss evaluated 24 hours after traumatic brain injury in mice. Compound 12 or vehicle was given s.c. 5 minutes post-injury. dagger

dagger dagger P<0.001 versus uninjured mice; *P<0.05 versus vehicle-treated injured mice; ns: non-significant versus vehicle-treated injured mice.

FIG. 14 shows the effects of compound 12 (50 mu M) on population spike (PS) amplitude in hippocampal cells. Traces show PSs recorded prior to (left), or 5 min after starting perfusion with 50 mu M compound 12 (right). Results are typical of 3 experiments. Each trace is the average of 10 consecutively recorded field potentials; 0.03 Hz stimulation.

FIG. 15 shows the effects of compound 12 (50 mu M) on population spike (PS) amplitude in hippocampal cells; control slices (left), slices subjected to OGD (middle); and slices subjected OGD in 0.3 mM Ca2+. Each trace is the average of 10 consecutively recorded field potentials; 0.03 Hz stimulation.

FIG. 16 shows the effects of treatment with 0.3 M Ca2+, and NOS inhibitors 7-NI (100 mu M) and compound 12. Either protection by low Ca2+ concentration (0.3 mM) or compound 12 (50 mu M) shows preservation of population spike, while 7-NI (100 mu M) treatment did not preserve population spike in hippocampal slices.

FIG. 17 shows the effects of 0.3M Ca2+ (PROT), 7-NI (100 mu M) or compound 12 (50 mu M) on the preservation of mitochondrial respiration in hippocampal slices after 10 min of OGD.

FIG. 18 shows flow charts of the experimental designs used in the Chung Spinal Nerve Ligation (SNL) model assays (tactile allodynia and thermal hyperalgesia) for neuropathic pain.

FIG. 19 shows the effect of 30 mg/kg i.p. administration of compounds 32(+) and 32(-) on the reversal of thermal hyperalgesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

FIG. 20 shows the effect of 30 mg/kg i.p. administration of compounds 32(+) and 32(-) on the reversal of tactile allodynia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

FIG. 21 shows the dose response (3 mg/kg-30 mg/kg) of compound 12 on the reversal of thermal hyperalgesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

FIG. 22 shows the dose response (3 mg/kg-30 mg/kg) of compound 12 on the reversal of tactile hyperthesia in rats after L5/L6 spinal nerve ligation (Chung neuropathic pain model).

FIG. 23 is a bar graph showing the effects of various NOS inhibitors (i.v.) or Sumatriptan succinate (s.c.) on the reversal of hindpaw allodynia in rats 2 hours after exposure of the dura with an inflammatory soup.

L9 ANSWER 22 OF 40 USPATFULL on STN
AN 2006:268571 USPATFULL
TI Nicotinamide riboside and analogues thereof
IN Milburn, Michael, Cary, NC, UNITED STATES
Milne, Jill, Brookline, MA, UNITED STATES
Normington, Karl D., Acton, MA, UNITED STATES
Nunes, Joseph J., Andover, MA, UNITED STATES
Salzmann, Thomas, Warren, NJ, UNITED STATES
Sinclair, David, West Roxbury, MA, UNITED STATES
Westphal, Christoph H., Brookline, MA, UNITED STATES
PA Sirtris Pharmaceuticals, Inc., Cambridge, MA, UNITED STATES (U.S. corporation)
PI US 20060229265 A1 20061012
AI US 2006-396359 A1 20060330 (11)

10574438

PRAI US 2005-667179P 20050330 (60)
DT Utility
FS APPLICATION
LN.CNT 6129
INCL INCLM: 514/043.000
INCLS: 514/342.000
NCL NCLM: 514/043.000
NCLS: 514/342.000
IC IPCI A61K0031-706 [I,A]; A61K0031-7042 [I,C*]; A61K0031-4436 [I,A]; A61K0031-4427 [I,C*]
IPCR A61K0031-7042 [I,C]; A61K0031-706 [I,A]; A61K0031-4427 [I,C]; A61K0031-4436 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 23 OF 40 USPATFULL on STN
AN 2006:241272 USPATFULL
TI Triazolopyrimidine derivatives as glycogen synthase kinase 3 inhibitors
IN Edgard Freyne, Eddy Jean, Beerse, BELGIUM
Love, Christopher John, Beerse, BELGIUM
Cooymans, Ludwig Paul, Beerse, BELGIUM
Vandermaesen, Nele, Beerse, BELGIUM
Buijnsters, Peter Jacobus Johannes Antonius, Beerse, BELGIUM
PI US 20060205721 A1 20060914
AI US 2004-564844 A1 20040712 (10)
WO 2004-EP51455 20040712
20060113 PCT 371 date
PRAI WO 2003-EP50310 20030716
DT Utility
FS APPLICATION
LN.CNT 3473
INCL INCLM: 514/234.500
INCLS: 514/252.020; 514/252.160; 514/261.100; 544/114.000; 544/238.000; 544/254.000
NCL NCLM: 514/234.500
NCLS: 514/252.020; 514/252.160; 514/261.100; 544/114.000; 544/238.000; 544/254.000
IC IPCI A61K0031-5377 [I,A]; A61K0031-5375 [I,C*]; A61K0031-519 [I,A]; C07D0487-02 [I,A]; C07D0487-00 [I,C*]
IPCR A61K0031-5375 [I,C]; A61K0031-5377 [I,A]; A61K0031-519 [I,C]; A61K0031-519 [I,A]; A61P0003-00 [I,C*]; A61P0003-10 [I,A]; A61P0025-00 [I,C*]; A61P0025-24 [I,A]; C07D0487-00 [I,C]; C07D0487-02 [I,A]; C07D0487-04 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 24 OF 40 USPATFULL on STN
AN 2006:215591 USPATFULL
TI Triazolopyrimidine derivatives as glycogen synthase kinase 3 inhibitors
IN Freyne, Eddy Jean Edgard, Rumst, BELGIUM
Love, Christopher John, Deurne, BELGIUM
Cooymans, Ludwig Paul, Beerse, BELGIUM
Vandermaesen, Nele, Olmen, BELGIUM
Buijnsters, Peter Jacobus Johannes Antonius, Breda, NETHERLANDS
Willems, Marc, Vosselaar, BELGIUM
Embrechts, Werner Constant Johan, Beerse, BELGIUM
PI US 20060183747 A1 20060817
AI US 2004-565065 A1 20040712 (10)
WO 2004-EP51457 20040712

20060117 PCT 371 date
PRAI   EP 2003-350314   20030716
DT   Utility
FS   APPLICATION
LN.CNT 3302
INCL   INCLM: 514/252.020
       INCLS: 514/255.050; 514/261.100; 544/238.000; 544/254.000
NCL   NCLM: 514/252.020
       NCLS: 514/255.050; 514/261.100; 544/238.000; 544/254.000
IC   IPCI   A61K0031-519 [I,A]; C07D0487-02 [I,A]; C07D0487-00 [I,C*]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9   ANSWER 25 OF 40 USPATFULL on STN
AN   2006:61200 USPATFULL
TI   Methods and compositions for treating nociceptive pain
IN   Meyerson, Laurence R., Las Vegas, NV, UNITED STATES
       Went, Gregory T., Mill Valley, CA, UNITED STATES
       Burkoth, Timothy S., San Francisco, CA, UNITED STATES
PI   US 20060052370   A1 20060309
AI   US 2005-211900   A1 20050824 (11)
PRAI   US 2004-603903P   20040824 (60)
DT   Utility
FS   APPLICATION
LN.CNT 1202
INCL   INCLM: 514/223.500
       INCLS: 514/282.000; 514/662.000; 514/674.000
NCL   NCLM: 514/223.500
       NCLS: 514/282.000; 514/662.000; 514/674.000
IC   IPCI   A61K0031-5415 [I,A]; A61K0031-485 [I,A]; A61K0031-13 [I,A]
       IPCR   A61K0031-5415 [I,A]; A61K0031-13 [I,C]; A61K0031-13 [I,A];
              A61K0031-485 [I,C]; A61K0031-485 [I,A]; A61K0031-5415 [I,C]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9   ANSWER 26 OF 40 USPATFULL on STN
AN   2005:159025 USPATFULL
TI   Combination of flupirtine and tramadol
IN   Szelenyi, Istvan, Schwaig, GERMANY, FEDERAL REPUBLIC OF
       Maus, Joachim, Muhlheim, GERMANY, FEDERAL REPUBLIC OF
       Cnota, Peter J., Homburg, GERMANY, FEDERAL REPUBLIC OF
PI   US 20050137235   A1 20050623
AI   US 2004-2762   A1 20041203 (11)
PRAI   US 2003-529761P   20031217 (60)
DT   Utility
FS   APPLICATION
LN.CNT 504
INCL   INCLM: 514/352.000
       INCLS: 514/650.000
NCL   NCLM: 514/352.000
       NCLS: 514/650.000
IC   [7]
       ICM   A61K031-44
       ICS   A61K031-138
       IPCI   A61K0031-44 [ICM,7]; A61K0031-138 [ICS,7]
       IPCR   A61K0031-137 [I,C*]; A61K0031-137 [I,A]; A61K0031-445 [I,C*];
              A61K0031-445 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 27 OF 40 USPATFULL on STN DUPLICATE 3
AN 2004:38089 USPATFULL
TI Transdermal delivery of analgesics
IN Klose, Kathryn Traci-Jane, Chelsea, AUSTRALIA
Colagrande, Felicia Maria, Brunswick, AUSTRALIA
Morgan, Timothy Matthias, Carlton North, AUSTRALIA
Finnin, Barrie Charles, Glen Iris, AUSTRALIA
Reed, Barry Leonard, Strathmore, AUSTRALIA
PA Monash University (non-U.S. corporation)
PI US 20040028625 A1 20040212
US 6916486 B2 20050712
AI US 2003-428012 A1 20030502 (10)
RLI Continuation-in-part of Ser. No. US 2001-910780, filed on 24 Jul 2001, PENDING Division of Ser. No. US 1998-125436, filed on 18 Dec 1998, GRANTED, Pat. No. US 6299900 A 371 of International Ser. No. WO 1997-AU91, filed on 19 Feb 1997, UNKNOWN
PRAI AU 1996-8144 19960219
DT Utility
FS APPLICATION
LN.CNT 574
INCL INCLM: 424/059.000
INCLS: 424/449.000
NCL NCLM: 424/448.000; 424/059.000
NCLS: 424/449.000; 514/974.000
IC [7]
ICM A61K007-42
ICS A61K009-70
IPCI A61K0007-42 [ICM,7]; A61K0009-70 [ICS,7]
IPCI-2 A61F0013-02 [ICM,7]
IPCR A61K0008-04 [I,C*]; A61K0008-04 [I,A]; A61K0008-30 [I,C*]; A61K0008-368 [I,A]; A61K0008-37 [I,A]; A61K0008-44 [I,A]; A61K0009-12 [I,C*]; A61K0009-12 [I,A]; A61K0031-4164 [I,C*]; A61K0031-4178 [I,A]; A61K0031-4196 [I,C*]; A61K0031-4196 [I,A]; A61K0031-496 [I,C*]; A61K0031-496 [I,A]; A61K0031-7028 [I,C*]; A61K0031-704 [I,A]; A61K0047-14 [I,C*]; A61K0047-14 [I,A]; A61L0015-16 [I,C*]; A61L0015-44 [I,A]; A61Q0017-04 [I,C*]; A61Q0017-04 [I,A]; A61K0009-00 [I,C*]; A61K0009-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 28 OF 40 USPATFULL on STN
AN 2004:127578 USPATFULL
TI Method for treating tension-type headache
IN Olesen, Jes, Hellerup, DENMARK
Bendtsen, Lars, Slagelse, DENMARK
Jensen, Rigmor, Virum, DENMARK
Madsen, Ulf, Horsholm, DENMARK
PI US 20040097562 A1 20040520
AI US 2003-702497 A1 20031107 (10)
RLI Division of Ser. No. US 2001-941855, filed on 30 Aug 2001, GRANTED, Pat. No. US 6649605 Division of Ser. No. US 1999-304115, filed on 4 May 1999, GRANTED, Pat. No. US 6284794 Continuation-in-part of Ser. No. WO 1997-DK502, filed on 4 Nov 1997, UNKNOWN
PRAI US 1998-85413P 19980514 (60)
US 1996-30294P 19961105 (60)
DT Utility
FS APPLICATION
LN.CNT 5241

INCL INCLM: 514/352.000
NCL NCLM: 514/352.000
IC [7]
ICM A61K031-44
IPCI A61K0031-44 [ICM,7]
IPCR A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 29 OF 40 USPATFULL on STN
AN 2004:100787 USPATFULL
TI Topical compositions and methods for treating pain
IN Williams, Robert O., Austin, TX, UNITED STATES
Zhang, Feng, Austin, TX, UNITED STATES
PA EpiCept Corporation (U.S. corporation)
PI US 20040076648 A1 20040422
AI US 2003-669258 A1 20030925 (10)
RLI Continuation of Ser. No. US 2001-931293, filed on 17 Aug 2001, GRANTED, Pat. No. US 6638981
DT Utility
FS APPLICATION
LN.CNT 2001
INCL INCLM: 424/400.000
INCLS: 514/220.000; 514/211.130; 514/225.200
NCL NCLM: 424/400.000
NCLS: 514/211.130; 514/220.000; 514/225.200
IC [7]
ICM A61K031-553
ICS A61K031-551; A61K031-5415
IPCI A61K0031-553 [ICM,7]; A61K0031-551 [ICS,7]; A61K0031-5415 [ICS,7]
IPCR A61K0009-107 [I,C*]; A61K0009-107 [I,A]; A61K0009-70 [I,C*]; A61K0009-70 [I,A]; A61K0031-137 [I,C*]; A61K0031-137 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0045-08 [I,A]; A61K0047-00 [I,C*]; A61K0047-00 [I,A]; A61K0047-06 [N,C*]; A61K0047-06 [N,A]; A61K0047-10 [I,C*]; A61K0047-10 [I,A]; A61K0047-14 [I,C*]; A61K0047-14 [I,A]; A61K0047-24 [N,C*]; A61K0047-24 [N,A]; A61K0047-26 [N,C*]; A61K0047-26 [N,A]; A61K0047-34 [N,C*]; A61K0047-34 [N,A]; A61K0047-44 [I,C*]; A61K0047-44 [I,A]; A61P0023-00 [I,C*]; A61P0023-02 [I,A]; A61P0025-00 [I,C*]; A61P0025-00 [I,A]; A61P0025-02 [I,A]; A61P0025-04 [I,A]; A61P0025-24 [I,A]; A61P0029-00 [I,C*]; A61P0029-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 30 OF 40 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2004:357431 SCISEARCH
GA The Genuine Article (R) Number: 810EK
TI Pharmacological characterisation of acid-induced muscle allodynia in rats
AU Nielsen A N (Reprint); Mathiesen C; Blackburn-Munro G
CS NeuroSearch AS, Dept Pharmacol, Pederstrupvej 93, DK-2750 Ballerup, Denmark (Reprint); NeuroSearch AS, Dept Pharmacol, DK-2750 Ballerup, Denmark
CYA Denmark
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (8 MAR 2004) Vol. 487, No. 1-3, pp. 93-103.
ISSN: 0014-2999.

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PB ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DT Article; Journal
LA English
REC Reference Count: 38
ED Entered STN: 30 Apr 2004
Last Updated on STN: 30 Apr 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

---Logging off of STN---

END

Unable to generate the STN prompt.
Exiting the script...

Jagoe